Supporting Information

Identification of Novel 1-*O*-substituted Aporphine Analogues as Potent 5-HT_{2C} Receptor Agonists

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General Information

^{1}H NMR spectra were recorded on 400 or 600 MHz (100 or 150 MHz for ^{13}C NMR) Agilent NMR spectrometer with $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts were reported in parts per million (ppm, δ scale) downfield from TMS at 0.00 ppm and referenced to the $CDCl_3$ at 7.26 ppm (for ^{1}H NMR) or 77.16 ppm (for ^{13}C NMR), the DMSO-d_6 at 2.50 ppm (for ^{1}H NMR) or 39.9 ppm (for ^{13}C NMR). HRMS was recorded on a GCT Premier TM (CI) Mass Spectrometer. Column chromatography was carried out on silica gel (200−300 mesh). All reactions were monitored using thin layer chromatography (TLC) on silica gel plates. All commercially available reagents, unless otherwise indicated, were used without further purification. The sample for detecting enantiomeric purity was free bases, while the sample for detecting optical rotation was hydrochloride salts. Enantiomeric purity was determined by chiral HPLC analysis on a Chiralpak IC column (250 × 4.6 mm, 5 μm, Lot No. IC00CE-RJ039, Part No 83325), eluting with n-Hexane/ EtOH /Diethylamine (95/5/0.05, v/v) at a flow rate of 0.8 mL min^{-1}. The sample injection volume was 20 μL. The detection wavelength was set at 270 nm.

Synthesis of Compounds 2a-b, 8, 9a, 13b, 14b, 15a-b, and 18a-k

6',7'-Dimethoxy-3',4'-dihydro-2'H-spiro[cyclobutane-1,1'-isoquinoline] (**2a**)

Cyclobutanone (2.0 mL, 3.2 mmol) was added slowly to a solution of 2-(3,4-dimethoxyphenyl)ethan-1-amine **1** (300 mg, 1.65 mmol) in phosphoric acid (5 mL), and the reaction was then heated under reflux for 24 h. The cooled mixture was poured carefully into ice water (50 mL) and basified using concentrated sodium hydroxide solution with vigorous stirring, and then extracted with DCM (25 mL × 2). The combined organic extracts were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 40:1) to yield the desired product **2a** (132 mg, 34%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.53 (s, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.06 (t, *J* = 5.7 Hz, 2H), 2.70 (t, *J* = 5.7 Hz, 2H), 2.51 – 2.43 (m, 2H), 2.22 – 2.10 (m, 3H), 2.06 – 1.98 (m, 1H), 1.80 (s, 1H). HRMS (CI) calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494, found 234.1492.

6',7'-Dimethoxy-3',4'-dihydro-2'H-spiro[cyclohexane-1,1'-isoquinoline] (**2b**)

Cyclohexanone (0.3 mL, 2.48 mmol) was added slowly to a solution of amine **1** (300 mg, 1.65 mmol) in phosphoric acid (5 mL), and the reaction was then heated under reflux for 48 h. The cooled mixture was poured carefully into ice water (50 mL), and basified using concentrated sodium hydroxide solution with vigorous stirring, and then extracted with DCM (25 mL × 2). The combined organic extracts were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 80:1) to yield the desired product **2b**

(117 mg, 27%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.56 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.05 (t, *J* = 5.7 Hz, 2H), 2.71 (t, *J* = 5.6 Hz, 2H), 1.81 – 1.59 (m, 10H), 1.34 – 1.27 (m, 1H). HRMS (CI) calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1807, found 262.1797.

4-(2-Isocyanatoethyl)-1,2-dimethoxybenzene (**4**)

A solution of triphosgene (534 mg, 1.79 mmol) in DCM was prepared under nitrogen atmosphere in a dry round bottom flask and cooled to 0 °C. The solution of amine **1** (813 mg, 4.48 mmol) and trimethylamine (1.86 mL, 13.44 mmol) in DCM under nitrogen atmosphere was then added dropwise. The ice bath was removed after 15 minutes and the reaction mixture was stirred for 1 h at room temperature. After removing trimethylamine hydrochloride by a plug of silica gel, the solvent was evaporated in vacuo to afford isocyanate **4** (300 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.1 Hz, 1H), 6.75 – 6.69 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.82 (t, *J* = 6.7 Hz, 2H).

Methyl (S)-2-(2-chlorophenyl)-2-hydroxyacetate (**5**)

To a solution of (*S*)-(+)-2-chloromandelic acid **3** (200 mg, 1.07 mmol) in MeOH (2 mL) was added $SOCl_2$ (0.09 mL, 1.18 mmol) at 0 °C under nitrogen atmosphere. After being stirred at room temperature for 16 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL). The mixture was then evaporated in vacuo to remove MeOH. The aqueous layer was extracted with EtOAc (50 mL× 2), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4,

filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/PE = 1:2) to afford the desired product **5** (192 mg, 90%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.37 – 7.26 (m, 2H), 5.60 (s, 1H), 5.32 (s, 1H), 3.80 (s, 3H).

Methyl (R)-2-(2-chlorophenyl)-2-(((3,4-dimethoxyphenethyl)carbamoyl)oxy) acetate (**6**)

A solution of **4** (102 mg, 0.49 mmol) and **5** (98 mg, 0.49 mmol) in toluene (0.5 mL) was refluxed overnight. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (PE/EtOAc = 2:1) to afford the desired product **6** (108 mg, 62%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 2H), 7.30 – 7.21 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 6.0 Hz, 2H), 6.42 (s, 1H), 5.05 (s, 1H), 3.82 (s, 6H), 3.72 (s, 3H), 3.41 (d, *J* = 6.3 Hz, 2H), 2.74 (t, *J* = 6.7 Hz, 2H).

(1S,10bS)-1-(2-chlorophenyl)-8,9-dimethoxy-1,5,6,10b-tetrahydro-3H-oxazolo[4, 3-a]isoquinolin-3-one (**7**)

To a solution of **6** (85 mg, 0.21 mmol) in anhydrous toluene (5 mL) was added dropwise DIBAL-H (1.5 M in toluene, 0.28 mL, 0.42 mmol) at −78 °C under nitrogen atmosphere, and stirred at −78 °C for 1 h. MeOH (0.16 mL) was then added, and the reaction was stirred at −20 °C for 10 min. Following the addition of $BF_3{\cdot}OEt_2$ (0.26 mL, 2.08 mmol), the resulting mixture was stirred at room temperature for another 1 h. This reaction mixture was quenched with H_2O (5 mL), evaporated in vacuo to remove

excess MeOH, and then partitioned between H_2O (50 mL) and EtOAc (50 mL). After neutralized with saturated aqueous $NaHCO_3$, the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 2:1) to provide the mixture (47 mg). The product was recrystallized to give the enantiomerically pure product **7** (29 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.33 (m, 2H), 6.77 (s, 1H), 6.61 (s, 1H), 5.76 (d, *J* = 4.6 Hz, 1H), 4.81 (d, *J* = 4.2 Hz, 1H), 4.13 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.18 (td, *J* = 12.5, 3.5 Hz, 1H), 3.13 – 3.03 (m, 1H),2.63 – 2.59 (m, 1H). HRMS (CI) calcd for $C_{19}H_{19}ClNO_4$ $[M+H]^+$: 360.1003, found 360.1007.

(S)-(2-chlorophenyl)((S)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (**8**)

To a solution of **7** (71 mg, 0.2 mmol) in 1.0 mL of EtOH was added 1.0 mL of water and pellets of potassium hydroxide (45 mg, 0.8 mmol). The resulting solution was then heated to reflux overnight. The solvent was removed in vacuo and the resulting residue was extracted with EtOAc (50 mL). The organic extracts were washed with brine，dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (DCM/MeOH = 20:1) to yield the desired product **8** (50 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.30 (m, 2H), 7.29 (d, *J* = 9.1 Hz, 1H), 6.62 (s, 1H), 6.44 (s, 1H), 5.36 (d, *J* = 4.0 Hz, 1H), 4.20 (d, *J* = 3.6 Hz, 1H), 3.89 (s, 3H), 3.69 (s, 3H), 3.31 – 3.26 (m, 1H), 3.08 – 3.01 (m, 1H), 2.93 – 2.85 (m, 1H), 2.73 – 2.66 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 147.8, 147.2, 139.9, 132.9, 129.4, 128.6,

128.3, 128.0, 126.9, 126.5, 111.5, 109.5, 72.0, 59.4, 55.8, 56.0, 43.0, 29.2. HRMS (CI) calcd for $C_{18}H_{21}ClNO_3$ $[M+H]^+$: 334.1210, found 334.1200.

(S)-1-(2-chlorobenzoyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-5,8-dione (**9a**)

Compound **8** (220 mg, 0.66 mmol) was dissolved in DCM (1.0 mL). To this solution was added di-*tert*-butyl dicarbonate (0.21 mL, 0.87 mmol) and stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure, and diluted with EtOAc (30 mL). The aqueous solution was extracted with EtOAc (30 mL × 2), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EtOAc = 1:1), giving pure product (259 mg, 90 %) as a white solid.

To a solution of above white solid (259 mg, 0.6 mmol) and Dess−Martin periodinane (509 mg, 1.2 mmol) was added DCM (20 mL) under nitrogen atmosphere. The reaction was stirred at room temperature for 1 h. After being quenched by the addition of 1 M $Na_2S_2O_3$ (aq), the aqueous layer was extracted with DCM (20 mL × 2). Following neutralized with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 2:1), giving pure product (220 mg, 79 %) as a yellow oil.

To remove the Boc protective group, above yellow oil (220 mg, 0.51 mmol) was dissolved in 1:2 (v/v) mix of HCl/EtOAc (6 mL) and stirred at room temperature for 1

h. After concentrated and neutralized with ammonia, the reaction mixture was extracted with DCM (30 mL × 2). The combined organic phases were then washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum to give the residue. The residue was purified by column chromatography on silica gel (PE/EtOAc = 2:1) to provide the desired product **9a** (85 mg, 46%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.40 – 7.34 (m, 2H), 6.73 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.82 (d, *J* = 7.8 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.1, 164.0, 151.6, 147.5, 138.1, 132.6, 131.6, 131.0, 130.0, 127.0, 118.9, 113.0, 110.1, 56.1, 56.0, 48.0, 25.1. HRMS (ESI) calcd for $C_{18}H_{16}ClKNO_5$ $[M+K]^+$: 400.0349, found 400.0362.

General Procedure for the Synthesis of Amides 12a-f

A solution of phenethylamine derivatives **11a-f** (1.0 eq), 2-(2-bromophenyl) acetic acid **10** (1.2 eq), and HOBt (1.2 eq) in DCM (0.2 M) was treated with EDCI (1.2 eq), and the resulting reaction mixture was stirred at room temperature 24 h. The mixture was partitioned by DCM and water. The oil layer was washed with 1 N HCl, saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The product was purified by recrystallization of the residue.

2-(2-Bromophenyl)-N-(3-methoxyphenethyl) acetamide (**12a**)

12a was prepared according to the general procedure with **11a** (1.26 mL, 8.50 mmol) as a white solid (2360 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 7.8 Hz,

1H), 6.66 (s, 2H), 5.44 (s, 1H), 3.79 (s, 3H), 3.69 (s, 2H), 3.50 (q, *J* = 6.1 Hz, 2H), 2.75 (t, *J* = 6.4 Hz, 2H).

2-(2-Bromophenyl)-N-(4-methoxyphenethyl) acetamide (**12b**)

12b was prepared according to the general procedure with **11b** (0.63 mL, 4.25 mmol) as a white solid (1180 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.17 – 7.12 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 5.40 (s, 1H), 3.77 (s, 3H), 3.66 (s, 2H), 3.43 (q, *J* = 6.5 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H).

N-(3-(benzyloxy)-4-propoxyphenethyl)-2-(2-bromophenyl) acetamide (**12c**)

12c was prepared according to the general procedure with **11c** (518 mg, 1.82 mmol) as a white solid (516 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 7.0 Hz, 1H), 7.26 (d, *J* = 3.2 Hz, 2H), 7.16 – 7.11 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 5.40 (s, 1H), 5.08 (s, 2H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.65 (s, 2H), 3.42 (q, *J* = 6.2 Hz, 2H), 2.66 (t, *J* = 6.6 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H).

N-(3-(benzyloxy)-4-(cyclopropylmethoxy)phenethyl)-2-(2-bromophenyl)acetamid e (**12d**)

12d was prepared according to the general procedure with **11d** (1550 mg, 5.23 mmol) as a white solid (2130 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.31 (d, *J* = 7.1 Hz,

1H), 7.26 (s, 2H), 7.15 – 7.11 (m, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.68 (s, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.36 (s, 1H), 5.09 (s, 2H), 3.84 (d, *J* = 6.9 Hz, 2H), 3.64 (s, 2H), 3.44 – 3.39 (m, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 1.35 – 1.26 (m, 1H), 0.62 (q, *J* = 7.5 Hz, 2H), 0.35 (q, *J* = 4.7 Hz, 2H).

2-(2-Bromophenyl)-N-(4-fluoro-3-methoxyphenethyl) acetamide (**12e**)

12e was prepared according to the general procedure with **11e** (1230 mg, 7.30 mmol) as a white solid (2000 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 4.2 Hz, 2H), 7.18 – 7.14 (m, 1H), 6.90 (dd, *J* = 11.1, 8.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.58 – 6.53 (m, 1H), 5.42 (s, 1H), 3.84 (s, 3H), 3.67 (s, 2H), 3.47 (q, *J* = 6.6 Hz, 2H), 2.72 (t, *J* = 6.8 Hz, 2H).

2-(2-Bromophenyl)-N-(4-chloro-3-methoxyphenethyl) acetamide (**12f**)

12f was prepared according to the general procedure with **11f** (2540 mg, 13.67 mmol) as a white solid (4770 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.26 (m, 2H), 7.19 – 7.14 (m, 2H), 6.67 (s, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.40 (s, 1H), 3.85 (s, 3H), 3.67 (s, 2H), 3.48 (q, *J* = 6.4 Hz, 2H), 2.73 (d, *J* = 6.8 Hz, 2H).

General Procedure for the Synthesis of Amines 13a-f

Method A: A solution of the amide **12a**, **12e-f** (1.0 eq) and $POCl_3$ (5.0 eq) in anhydrous acetonitrile (0.2 M) was refluxed for 3 h, After working up, the solution was neutralized with a saturated aqueous $NaHCO_3$. The resulting mixture was extracted with DCM (50 mL × 2), concentrated in vacuum, and then redissolved in

MeOH (0.2 M). $NaBH_4$ (3.0 eq) was added to the mixture by portion under ice bath. The resulting mixture was stirred for 3h at room temperature. The mixture was partitioned by DCM and water. The oil layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH/NH_4OH (50-100:1:0.5) as the eluent to give **13a**, **13e-f**.

Method B: The compound amide **12b** (1.0 eq) and P_2O_5 (5.0 eq) were refluxed in toluene for 3 h. Following neutralized with saturated aqueous $NaHCO_3$, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was then redissolved in MeOH (0.2 M). $NaBH_4$ was added to the mixture under an 0 ℃, and stirred for 3h at room temperature. The mixture was partitioned by DCM and water. The oil layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH/NH_4OH (50-100:1:0.5) as the eluent to give **13b**.

Method C: To a solution of the amide **12c-d** (1.0 eq) in DCM (0.2 M) in a round-bottomed flask was added PCl_5 (3.0 eq), and the resulting mixture was refluxed for 20 mins. The reaction was then cooled to 0 °C, and neutralized with a saturated aqueous $NaHCO_3$. The resulting mixture was extracted with DCM (50 mL × 2) to afford the crude product. These compounds were found to be unstable and decomposed on standing or exposure to silica gel. They were thus used without

further purification immediately. To a solution of the previous crude (1.0 eq) in MeOH (0.2 M) at 0°C was added slowly $NaBH_4$ (3.0 eq). The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was extracted with DCM and the oil layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using DCM/MeOH/NH_4OH (50-100:1:0.5) as the eluent to give **13c-d**.

1-(2-Bromobenzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**13a**)

13a was prepared according to the general procedure (**Method A**) with **12a** (1610 mg, 4.64 mmol) as a colorless oil (1070 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.30 (d, *J* = 4.2 Hz, 2H), 7.28 (s, 1H), 7.18 – 7.12 (m, 1H), 6.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.68 (s, 1H), 4.32 (d, *J* = 10.2Hz, 1H), 3.82 (s, 3H), 3.42 (dd, *J* = 13.6, 3.0 Hz, 1H), 3.30 – 3.24(m, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.77 (m, 2H), 1.78 (s, 1H).

1-(2-Bromobenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline **(13b)**

13b was prepared according to the general procedure (**Method B**) with **12b** (348 mg, 1 mmol) as a colorless oil (234 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 4.2 Hz, 2H), 7.16 – 7.11 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 6.76 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.31 (d, *J* = 9.8 Hz, 1H), 3.79 (s, 3H), 3.41 (dd, *J* = 13.7, 3.1 Hz, 1H), 3.28 – 3.22(m, 1H), 3.03 – 2.94 (m, 2H), 2.82 – 2.73 (m, 2H), 1.83 (s, 1H).

6-(Benzyloxy)-1-(2-bromobenzyl)-7-propoxy-1,2,3,4-tetrahydroisoquinoline (**13c**)

13c was prepared according to the general procedure (**Method C**) with **12c** (241 mg, 0.5 mmol) as a colorless oil (162 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 4.2 Hz, 2H), 7.16 – 7.12 (m, 1H), 6.82 (s, 1H), 6.68 (s, 1H), 5.12 (s, 2H), 4.26 (d, *J* = 7.8 Hz, 1H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.37 (dd, *J* = 13.5, 2.7 Hz, 1H), 3.27 – 3.21 (m, 1H), 3.02 – 2.93 (m, 2H), 2.74 – 2.69 (m, 2H), 1.88 – 1.83 (m, 2H), 1.75 (s, 1H), 1.07 (t, *J* = 7.3 Hz, 3H).

6-(Benzyloxy)-1-(2-bromobenzyl)-7-(cyclopropylmethoxy)-1,2,3,4-tetrahydroisoquinoline (**13d**)

13d was prepared according to the general procedure (**Method C**) with **12d** (494 mg, 1 mmol) as a colorless oil (315 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.17 – 7.08 (m, 1H), 6.84 (s, 2H), 6.67 (s, 2H), 5.13 (s, 2H), 4.26 (dd, *J* = 9.7, 2.5 Hz, 1H), 3.84 (d, *J* = 6.9 Hz, 2H), 3.36 (dd, *J* = 13.6, 3.3 Hz, 1H), 3.27 – 3.20(m, 1H), 3.01 – 2.92 (m, 2H), 2.76 – 2.65 (m, 2H), 1.72 (s, 1H), 1.34 – 1.26 (m, 1H), 0.62 (q, *J* = 7.6 Hz, 2H), 0.35 (q, *J* = 4.6 Hz, 2H).

1-(2-Bromobenzyl)-7-fluoro-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**13e**)

13e was prepared according to the general procedure (**Method A**) with **12e** (366 mg, 1 mmol) as a colorless oil (152 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d,

J = 7.9 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.16 – 7.11 (m, 1H), 7.05 (d, *J* = 12.3 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 4.23 (d, *J* = 9.6 Hz, 1H), 3.87 (s, 3H), 3.34 (dd, *J* = 13.5, 2.0 Hz, 1H), 3.27 – 3.21(m, 1H), 2.98 – 2.89 (m, 2H), 2.82 – 2.68 (m, 2H), 1.68 (s, 1H).

1-(2-Bromobenzyl)-7-chloro-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**13f**)

13f was prepared according to the general procedure (**Method A**) with **12f** (1450 mg, 3.79 mmol) as a colorless oil (1000 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.29 – 7.25 (m, 3H), 7.16 – 7.11 (m, 1H), 6.66 (s, 1H), 4.26 (d, *J* = 10.2 Hz, 1H), 3.88 (s, 3H), 3.36 (dd, *J* = 13.6, 3.1 Hz, 1H), 3.28 – 3.22 (m, 1H), 2.99 – 2.92 (m, 2H), 2.84 – 2.75 (m, 2H), 2.38 (s, 1H).

1-(2-Bromobenzyl)-7-methoxy-2-propyl-1,2,3,4-tetrahydroisoquinoline (**14b**)

A solution of **13b** (537 mg, 1.62 mmol), PrBr (497 mg, 4.04 mmol), KI (538 mg, 3.24 mmol) and K_2CO_3 (892 mg, 6.45 mmol) in acetone (0.2 M) was refluxed for 4 h. The reaction mixture was diluted with DCM and water. The aqueous layer was extracted with DCM (30 mL × 3), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using PE/EtOAc (4:1) as eluant to give **14b** as a colorless oil (198 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.15 – 7.06(m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.42 (s, 1H), 4.00 (t, *J* = 7.0 Hz, 1H), 3.65 (s, 3H), 3.43 – 3.34 (m, 1H), 3.20 – 3.15(m, 1H), 3.07 (dd, *J* = 13.3, 5.9 Hz, 1H), 3.00 – 2.88 (m, 2H), 2.57 – 2.44 (m, 3H), 1.41 – 1.24 (m, 2H), 0.72 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

157.1, 139.6, 138.7, 132.9, 132.5, 129.8, 127.7, 126.8, 126.6, 124.9, 113.0, 112.8, 60.6, 55.5, 55.1, 43.9, 42.3, 23.4, 21.2, 11.6. HRMS (CI) calcd for $C_{20}H_{25}BrNO$ $[M+H]^+$: 374.1120, found 374.1123.

3-Methoxy-5,6,12,12a-tetrahydroindolo[2,1-a] isoquinoline (**15a**)

K_2CO_3 (150 mg, 2 mmol), PhDavePhos (17.5 mg, 0.05 mmol), $Pd(OAc)_2$ (5.5 mg, 0.03 mmol) and **14a** (180 mg, 0.54 mmol) were weighed and placed in a round-bottomed flask. The flask was purged with nitrogen atmosphere. DMA (0.2 M) was then added, and the resulting mixture was heated to 130 °C for 4 h. The reaction mixture was concentrated, and the residue was purified using a silica gel column eluted with PE/EtOAc (20:1) to afford **15a** (102 mg, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.4 Hz, 1H), 7.08 – 7.03 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.70 – 6.56 (m, 2H), 6.54 (s, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 3.87 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.75 (s, 3H), 3.55 – 3.49 (m, 1H), 3.37 – 3.31 (m, 1H), 3.16 – 3.00 (m, 2H), 2.56 – 2.52 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.8, 150.4, 136.2, 131.4, 129.7, 127.3, 127.0, 124.9, 118.0, 113.3, 112.8, 107.4, 62.4, 55.2, 42.1, 36.9, 25.7. HRMS (CI) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388, found 252.1385.

2-Methoxy-5,6,12,12a-tetrahydroindolo[2,1-a] isoquinoline (**15b**)

15b was prepared in the same manner as described in synthesis of **15a** starting from **14b** (205 mg, 0.62mmol) as a colorless oil (93 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.03 (m, 2H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.72 – 6.60 (m, 4H), 4.84 (d, *J* = 6.7 Hz, 1H), 3.87 (dd, *J* = 13.2, 4.9 Hz, 1H), 3.78 (s, 3H), 3.57 – 3.50 (m, 1H),

3.38 – 3.25 (m, 1H), 3.16 – 3.12 (m, 1H), 3.06 – 2.92 (m, 1H), 2.52 – 2.48(m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 150.5, 140.5, 129.7, 129.5, 127.4, 127.1, 124.9, 118.1, 112.3, 111.1, 107.4, 63.0, 55.3, 42.4, 36.9, 24.6. HRMS (CI) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388, found 252.1382.

General Procedure for the Synthesis of 16a-f

TEA (2.5 eq) was added to a solution of **13a-f** (1.0 eq) in DCM (0.2 M) at room temperature. The mixture was cooled to 0 ℃, and trifluoroacetic anhydride (TFAA) (1.2 eq) was added dropwise to the mixture. After the addition, the reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with DCM (50 mL). The mixture was then washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The resulting residue was purified using a silica gel column eluted with PE/EtOAc (10:1) to afford **16a-f**.

1-(1-(2-Bromobenzyl)-6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluor oethan-1-one (**16a**)

16a was prepared according to the general procedure with **13a** (612 mg, 1.84 mmol) as a white solid (548 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 3H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.66 (s, 1H), 5.85 (dd, *J* = 9.2, 4.9 Hz, 1H), 4.05 – 4.01(m, 1H), 3.80 (s, 3H), 3.78 –

3.71 (m, 1H), 3.41 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.18 – 3.12(m, 1H), 3.03 – 2.94 (m, 1H), 2.89 – 2.81 (m, 1H).

1-(1-(2-Bromobenzyl)-7-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2,2-trifluor oethan-1-one (**16b**)

16b was prepared according to the general procedure with **13b** (1320 mg, 3.98 mmol) as a white solid (1360 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.09(m, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.66 (s, 1H), 5.86 (dd, *J* = 9.2, 5.2 Hz, 1H), 4.06 – 4.03m, 1H), 3.81 – 3.74 (m, 1H), 3.73 (s, 3H), 3.44 (dd, *J* = 13.8, 5.1 Hz, 1H), 3.21 – 3.16(m, 1H), 3.01 – 2.90 (m, 1H), 2.87 – 2.79 (m, 1H).

1-(6-(Benzyloxy)-1-(2-bromobenzyl)-7-propoxy-3,4-dihydroisoquinolin-2(1H)-yl) -2,2,2-trifluoroethan-1-one (**16c**)

16c was prepared according to the general procedure with **13c** (171 mg, 0.37 mmol) as a white solid (160 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.33 – 7.29 (m, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.14 – 7.06 (m, 2H), 6.65 (s, 1H), 6.55 (s, 1H), 5.83 – 5.72 (m, 1H), 5.11 (s, 2H), 4.03 – 3.99(m, 1H), 3.88 – 3.80 (m, 2H), 3.78 – 3.69 (m, 1H), 3.39 (dd, *J* = 13.6, 5.5 Hz, 1H), 3.19 – 3.14(m, 1H), 2.97 – 2.86 (m, 1H), 2.79 – 2.70 (m, 1H), 1.85 – 1.76 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H).

1-(6-(Benzyloxy)-1-(2-bromobenzyl)-7-(cyclopropylmethoxy)-3,4-dihydroisoquin olin-2(1H)-yl)-2,2,2-trifluoroethan-1-one (**16d**)

16d was prepared according to the general procedure with **13d** (1280 mg, 2.68mmol) as a white solid (1146 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.34 – 7.30 (m, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.04 (m, 2H), 6.66 (s, 1H), 6.57 (s, 1H), 5.85 – 5.71 (m, 1H), 5.13 (s, 2H), 4.03 – 4.00(m, 1H), 3.78 – 3.68 (m, 3H), 3.39 (dd, *J* = 13.5, 5.4 Hz, 1H), 3.20 – 3.14 (m, 1H), 2.96 – 2.86 (m, 1H), 2.80 – 2.71 (m, 1H), 1.32 – 1.22 (m, 1H), 0.63 (q, *J* = 7.3 Hz, 2H), 0.34 (q, *J* = 4.6 Hz, 2H).

1-(1-(2-Bromobenzyl)-7-fluoro-6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2, 2-trifluoroethan-1-one (**16e**)

16e was prepared according to the general procedure with **13e** (146 mg, 0.42 mmol) as a white solid (140 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 2H), 6.88 (d, *J* = 11.7 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 1H), 5.80 (dd, *J* = 9.0, 4.7 Hz, 1H), 4.47 – 4.04(m, 1H), 3.88 (s, 3H), 3.75 – 3.67 (m, 1H), 3.40 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.16 – 3.10(m, 1H), 3.02 – 2.91 (m, 1H), 2.85 – 2.80(m, 1H).

1-(1-(2-Bromobenzyl)-7-chloro-6-methoxy-3,4-dihydroisoquinolin-2(1H)-yl)-2,2, 2-trifluoroethan-1-one (**16f**)

16f was prepared according to the general procedure with **13f** (1000 mg, 2.73 mmol) as a white solid (900 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.20(m, 1H), 7.15 – 7.07 (m, 3H), 6.67 (s, 1H), 5.82 (dd, *J* = 9.3, 4.9

Hz, 1H), 4.09 – 4.04(m, 1H), 3.89 (s, 3H), 3.78 – 3.67 (m, 1H), 3.40 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.17 – 3.11(m, 1H), 3.04 – 2.91 (m, 1H), 2.89 – 2.79 (m, 1H).

General Procedure for the Synthesis of 17a-f by Intramolecular Oxidative Cyclization

K_2CO_3 (2.0 eq), PhDavePhos (0.1 eq), $Pd(OAc)_2$ (0.05 eq) and the aryl halide **16a-f** (1.0 eq) were weighed and placed in a round-bottomed flask under nitrogen atmosphere. DMA (0.2 M) was then added, and the resulting mixture was heated to 130 °C for 4 h. The reaction mixture was concentrated. The resulting residue was purified using a silica gel column eluted with PE/EtOAc (10:1) to afford **17a-f**.

2,2,2-Trifluoro-1-(2-methoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)ethan-1-one (**17a**)

17a was prepared according to the general procedure with **16a** (540 mg, 1.26 mmol) as a white solid (185 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.28 (d, *J* = 4.0 Hz, 2H), 7.21 (s, 1H), 6.66 (s, 1H), 5.16 (dd, *J* = 13.9, 3.9 Hz, 1H), 4.25 – 4.22 (m, 1H), 3.86 (s, 3H), 3.42 – 3.34(m, 1H), 3.20 (dd, *J* = 13.8, 4.3 Hz, 1H), 3.01 – 2.79 (m, 3H).

2,2,2-Trifluoro-1-(1-methoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)ethan-1-one (**17b**)

17b was prepared according to the general procedure with **16b** (95 mg, 0.22 mmol) as a white solid (64 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.1 Hz, 1H), 7.35 – 7.20 (m, 3H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 5.12

(d, *J* = 13.5 Hz, 1H), 4.24 – 4.21 (m, 1H), 3.91 (s, 3H), 3.37 – 3.30 (m, 1H), 3.04 – 2.98 (m, 1H), 2.97 – 2.79 (m, 3H).

1-(2-(Benzyloxy)-1-propoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl) -2,2,2-trifluoroethan-1-one (**17c**)

17c was prepared according to the general procedure with **16c** (150 mg, 0.27 mmol) as a white solid (74 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.37 – 7.30 (m, 2H), 7.29 – 7.24 (m, 2H), 6.73 (s, 1H), 5.18 – 5.08(m, 2H), 5.03 (dd, *J* = 13.6, 3.1 Hz, 1H), 4.22 – 4.19 (m, 1H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.63 (q, *J* = 6.8 Hz, 1H), 3.35 – 3.32 (m, 1H), 3.05 (dd, *J* = 13.3, 3.6 Hz, 1H), 2.98 – 2.79 (m, 2H), 2.75 – 2.71 (m, 1H), 1.77 – 1.66 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

1-(2-(Benzyloxy)-1-(cyclopropylmethoxy)-4,5,6a,7-tetrahydro-6H-dibenzo[de,g] quinolin-6-yl)-2,2,2-trifluoroethan-1-one (**17d**)

17d was prepared according to the general procedure with **16d** (287 mg, 0.5 mmol) as a white solid (200 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 6.6 Hz, 2H), 7.42 (t, *J* = 6.9 Hz, 2H), 7.38 – 7.34 (m, 2H), 7.30 – 7.27 (m, 2H), 6.74 (s, 1H), 5.20 – 5.10(m, 2H), 5.07 – 5.03 (m, 1H), 4.22 (d, *J* = 12.7 Hz, 1H), 3.79 (t, *J* = 8.1 Hz, 1H), 3.47 (t, *J* = 8.2 Hz, 1H), 3.36 (t, *J* = 12.6 Hz, 1H), 3.06 (d, *J* = 13.2 Hz, 1H), 3.00 – 2.84 (m, 2H), 2.76 – 2.72 (m, 1H), 1.20 – 1.10 (m, 1H), 0.47 (d, *J* = 6.5 Hz, 2H), 0.17 – 0.09 (m, 2H).

2,2,2-Trifluoro-1-(1-fluoro-2-methoxy-4,5,6a,7-tetrahy dro-6H-dibenzo[de,g]quinolin-6-yl)ethan-1-one (**17e**)

17e was prepared according to the general procedure with **16e** (65 mg, 0.15 mmol) as a white solid (28 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.31 (d, *J* = 3.4 Hz, 2H), 6.71 (d, *J* = 7.5 Hz, 1H), 5.08 (d, *J* = 13.5 Hz, 1H), 4.26 – 4.22 (m, 1H), 3.92 (s, 3H), 3.35 (t, *J* = 12.8 Hz, 1H), 3.11 (dd, *J* = 13.6, 3.3 Hz, 1H), 2.99 – 2.76 (m, 3H).

1-(1-Chloro-2-methoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)-2,2, 2-trifluoroethan-1-one (**17f**)

17f was prepared according to the general procedure with **16f** (139 mg, 0.3 mmol) as a white solid (73 mg, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (d, *J* = 6.7 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.08 (s, 1H), 4.77 – 4.72(m, 1H), 4.14 – 4.10 (m, 1H), 3.90 (s, 3H), 3.50 – 3.40 (m,1H), 2.97 – 2.86 (m, 4H).

2,2,2-Trifluoro-1-(2-propoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)ethan-1-one (**17g**)

BBr_3 (1 M in DCM, 3 mL) was added dropwise to a solution of **17a** (347 mg, 1 mmol) in DCM (0.1 M) at -78 ℃ under nitrogen atmosphere. The reaction mixture was then allowed to warm to room temperature for 1 h. The reaction mixture was quenched with ice cold water, and extracted with anhydrous EtOAc (30 mL × 3). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. A solution of above product (100 mg, 0.3 mmol), PrBr (74 mg,

0.6 mmol), KI (100 mg, 0.6 mmol) and K_2CO_3 (83 mg, 0.6 mmol) in acetone (15 mL) was refluxed for 24 h. The reaction mixture was diluted with DCM (50 mL) and washed with water. The aqueous layer was extracted with DCM (50 mL× 2), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using PE/DCM (4:1) as the eluent to give **17g** (80 mg, 71%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.28 (d, *J* = 3.9 Hz, 2H), 7.22 (s, 1H), 6.66 (s, 1H), 5.17 (dd, *J* = 13.9, 3.8 Hz, 1H), 4.24 (d, *J* = 13.3 Hz, 1H), 4.02 – 3.94 (m, 2H), 3.38 (t, *J* = 12.6 Hz, 1H), 3.20 (dd, *J* = 13.8, 4.3 Hz, 1H), 3.02 – 2.78 (m, 3H), 1.89 – 1.80 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H).

Procedure for Synthesis of 18a-b, 18g and18j-k

To a round-bottomed flask were added compound **17a-b**, **17g, 17e-f** (1.0 eq) and EtOH (0.1 M). $NaBH_4$ (20.0 eq) were then added, and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1.5 h. Afterwards, the mixture of solvents was evaporated under reduced pressure, and brine was added to the residue, which was extracted with DCM (30 mL× 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtrated, and concentrated. The resulting residue was purified by column chromatography using DCM/MeOH/NH_4OH (20-50:1:0.5) as the eluent. The above purified product was stirred in a 1 N HCl solution in EtOAc at ambient temperature for 4-6 h. A white precipitate formed after several hours, and the

mixture was stirred until the reaction completed by TLC. The solvent was removed in vacuo to give the corresponding product **18a-b, 18g** and **18j-k** as a white solid.

2-Methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18a**)

18a was prepared according to the general procedure with **17a** (166 mg, 0.48 mmol) as a white solid (96 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 9.71 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 6.82 (s, 1H), 4.42 – 4.39 (m, 1H), 3.83 (s, 3H), 3.65 – 3.53 (m, 1H), 3.26 – 3.23 (m, 2H), 3.18 (dd, *J* = 14.2, 4.6 Hz, 1H), 3.05 – 2.93 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.8, 134.6, 133.3, 133.2, 129.1, 128.9, 128.4, 124.8, 121.0, 113.4, 109.2, 55.8, 51.8, 40.8, 32.6, 25.5. HRMS (CI) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388, found 252.1380.

1-Methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolone hydrochloride (**18b**)

18b was prepared according to the general procedure with **17b** (64 mg, 0.18 mmol) as a white solid (21 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 2H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.21 (m, 4H), 7.16 (d, *J* = 8.6 Hz, 1H), 4.32 (d, *J* = 10.6 Hz, 1H), 3.86 (s, 3H), 3.61 – 3.56 (m, 1H), 3.27 – 3.17 (m, 2H), 3.08 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.98 – 2.91(m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.6, 133.5, 131.7, 131.1, 129.7, 128.9, 128.4, 127.9, 127.5, 123.2, 121.1, 113.1, 56.4, 52.6, 40.6, 33.0, 24.7. HRMS (CI) calcd for $C_{17}H_{18}NO$ $[M+H]^+$: 252.1388, found 252.1392.

1-Propoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18g**)

18g was prepared according to the general procedure with **17g** (83 mg, 0.22

mmol) as a white solid (46 mg, 66%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (s, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 6.0 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.82 (s, 1H), 4.47 – 4.34 (m, 1H), 4.06 – 3.97 (m, 2H), 3.64 – 3.58 (m, 1H), 3.28 – 3.18 (m, 1H), 3.16 (dd, *J* = 14.2, 4.3 Hz, 1H), 3.03 – 2.93 (m, 2H), 1.82 – 1.67 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.2, 140.8, 134.6, 133.3, 133.1, 129.0, 128.8, 128.4, 124.8, 120.9, 114.0, 109.6, 69.6, 51.8, 40.8, 32.6, 25.5, 22.5, 10.8. HRMS (CI) calcd for $C_{19}H_{22}NO$ $[M+H]^+$: 280.1701, found 280.1703.

1-Fluoro-2-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolone hydrochloride (**18j**)

18j was prepared according to the general procedure with **17e** (30 mg, 0.08 mmol) as a white solid (20 mg, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (s, 2H), 7.92 (d, *J* = 6.8 Hz, 1H), 7.44 – 7.31 (m, 3H), 7.07 (d, *J* = 7.5 Hz, 1H), 4.32 (d, *J* = 13.4 Hz, 1H), 3.88 (s, 3H), 3.62 – 3.55 (m, 1H), 3.24 – 3.12 (m, 3H), 3.04 – 2.92 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 148.2 (d, *J* = 249.3 Hz), 148.1, 148.0, 134.0, 129.5, 129.1, 128.2, 128.1, 127.7, 122.1, 121.0 (d, *J* = 8.0 Hz), 113.2, 56.7, 51.6, 40.6, 33.0, 25.2. HRMS (CI) calcd for $C_{17}H_{17}FNO$ $[M+H]^+$: 270.1294, found 270.1297.

1-Chloro-2-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18k**)

18k was prepared according to the general procedure with **17f** (68 mg, 0.18mmol) as a white solid (40 mg, 70%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 2H), 8.21 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 7.1 Hz, 1H), 7.40 – 7.35(m, 2H), 7.07 (s, 1H), 4.19 (d,

J = 11.5 Hz, 1H), 3.90 (s, 3H), 3.59 (d, *J* = 4.6 Hz, 1H), 3.26 – 3.19 (m, 2H), 3.10 (d, *J* = 10.8 Hz, 1H), 3.03 – 2.88 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.4, 135.2, 132.2, 131.4, 129.2, 129.0, 128.7, 127.2, 124.4, 117.9, 112.0, 56.9, 52.3, 33.4, 25.3. HRMS (CI) calcd for $C_{17}H_{17}ClNO$ $[M+H]^+$: 286.0999, found 286.0989.

Procedure for the Synthesis of 18c-f

Step A: **For compounds 18c-d**: To a stirred solution of **17c-d** (1.0 eq) in 1:1 (v/v) mix of MeOH/DCM (0.2 M) was added 10% Pd/C (0.2 eq), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 4 h. The catalyst was removed by filtration and the filtrate was evaporated to give a residue. The resulting residue was purified using a silica gel column eluted with PE/EtOAc (5:1) to afford the product.

For compounds 18e-f: BBr_3 (1 M in DCM, 2.0 eq) was added dropwise to a solution of **17e-f** (1.0 eq) in DCM (0.2 M) at -78 °C under nitrogen atmosphere. The reaction mixture was then allowed to warm to room temperature for 1 h. The reaction was quenched with ice cold water, extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified using a silica gel column eluted with PE/ EtOAc (5:1) to afford the product.

Step B: To a solution of above product (1.0 eq) in DCM (0.2 M) was added trifluoromethanesulfonic anhydride (Tf_2O) (1.2 eq) and TEA (2.5 eq) at 0°C. The reaction mixture was stirred for 30 mins, and then quenched with water. The organic

layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified using a silica gel column eluted with PE/EtOAc (20:1) to afford the product. To a round-bottomed flask equipped with magnetic stirring bar charged with anhydrous DMF (0.2 M) and TEA (8.0 eq), 98% HCOOH (8.0 eq) was added dropwise over 1 minutes. Above product (1.0 eq) was then added followed by $Pd(OAc)_2$ (0.04 eq) and DPPF (0.08 eq). The mixture was heated to 60 °C. After 15 mins, the mixture was cooled to room temperature, added water (50 mL), and extracted with DCM (30 mL× 3). The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified using a silica gel column eluted with PE/EtOAc (10:1) to afford the product**.**

Step C: To a round-bottomed flask were added above product (1.0 eq) and EtOH (0.1 M). Then, $NaBH_4$ (20.0 eq) were added, and the reaction mixture was maintained at room temperature under nitrogen atmosphere for 1.5 h. Afterwards, the solvents was evaporated under reduced pressure, and brine was added to the residue, which was extracted with DCM (30 mL× 2). The organic phase was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure. The residue was then purified by column chromatography using DCM/MeOH/NH_4OH (20-50:1:0.5) as the eluent. The purified above product was dissolved in a 1N HCl solution in EtOAc, and the reaction mixture was stirred at ambient temperature for 4-6 h. A white precipitate formed after several hours, and the mixture was stirred until the reaction was complete by TLC. The solvent was removed in vacuo to give **18c-f**.

1-Propoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18c**)

18c was prepared according to the general procedure with 2,2,2-trifluoro-1-(1-propoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[de,g]quinolin-6-yl)ethan-1-one (30 mg, 0.08 mmol) as a white solid (15 mg, 60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (s, 2H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.31(m, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 4.32 (d, *J* = 10.8 Hz, 1H), 4.14 (q, *J* = 6.4 Hz, 1H), 3.90 (q, *J* = 6.5 Hz, 1H), 3.63 – 3.53 (m, 1H), 3.28 – 3.13 (m, 2H), 3.08 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.95 – 2.90 (m, 2H), 1.82 – 1.73 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 154.9, 133.5, 131.8, 131.1, 129.6, 128.9, 128.4, 127.9, 127.3, 123.1, 121.2, 113.9, 70.5, 52.6, 40.6, 33.1, 24.7, 22.6, 11.2. HRMS (CI) calcd for $C_{19}H_{22}NO$ $[M+H]^+$: 280.1701, found 280.1696.

1-(Cyclopropylmethoxy)-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18d**)

18d was prepared according to the general procedure with 1-(1-(cyclopropylmethoxy)-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)-2,2,2-trifluoroethan-1-one (49 mg, 0.13 mmol) as a white solid (30 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 9.54 (s, 1H), 8.38 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.04 – 3.92 (m, 1H), 3.92 – 3.82 (m, 1H), 3.58 (d, *J* = 6.8 Hz, 1H), 3.27 – 3.13 (m, 2H), 3.09 (dd, *J* = 13.9, 4.2 Hz, 1H), 2.95 – 2.90 (m, 2H), 1.30 – 1.23 (m, 1H), 0.60 – 0.57 (m, 2H), 0.39 – 0.28 (m, 2H). ^{13}C NMR (151 MHz,

DMSO-d_6) δ 154.9, 133.5, 131.8, 131.1, 129.6, 129.0, 128.4, 127.8, 127.4, 123.2, 121.3, 114.4, 73.4, 52.6, 40.6, 33.0, 24.7, 10.6, 3.5, 3.4. HRMS (CI) calcd for $C_{20}H_{22}NO$ $[M+H]^+$: 292.1701, found 292.1697.

1-Fluoro-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18e**)

18e was prepared according to the general procedure with 2,2,2-trifluoro-1-(1-fluoro-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)ethan-1-one (60 mg, 0.18 mmol) as a white solid (27 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 2H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.45 – 7.29 (m, 5H), 4.44 (dd, *J* = 13.8, 3.4 Hz, 1H), 3.62 – 3.57 (m, 1H), 3.29 – 3.26 (m, 2H), 3.21 – 3.17 (m, 1H), 3.11 – 2.93 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 158.3 (d, *J* = 248.1 Hz), 133.7, 131.6 (d, *J* = 3.1 Hz), 130.3 (d, *J* = 9.0 Hz), 129.4, 129.1, 128.3, 128.1, 128.0, 127.9, 120.5 (d, *J* = 11.0 Hz), 116.8 (d, *J* = 23.9 Hz), 52.1, 40.4, 32.5, 24.8. HRMS (CI) calcd for $C_{16}H_{15}FN$ $[M+H]^+$: 240.1189, found 240.1192.

1-Chloro-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolone hydrochloride (**18f**)

18f was prepared according to general procedure with 1-(1-chloro-4,5,6a,7-tetrahydro-6*H*-dibenzo[de,g]quinolin-6-yl)-2,2,2-trifluoroethan-1-one (45 mg, 0.13 mmol) as a white solid (27 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 2H), 8.20 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.26 (d, *J* = 8.3 Hz, 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 3.59 (d, *J* = 6.8 Hz, 1H), 3.29 – 3.19 (m, 2H), 3.13 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.03 – 2.92 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 134.8, 133.1, 131.2, 131.1, 131.0, 130.9, 129.9, 129.2,

128.8, 128.7, 128.6, 127.4, 52.6, 32.9, 24.9. HRMS (CI) calcd for $C_{16}H_{15}ClN$ $[M+H]^+$: 256.0893, found 256.0886.

Procedure for the Synthesis of **18h-i**

2-Chloro-1-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18h**)

17b (61mg, 0.18 mmol) was dissolved in Acetonitrile (3 mL), treated with N-chlorosuccinimide (47mg, 0.35mmol), and stirred at 70 °C for 2h. The product mixture was diluted with water (30 mL) and extracted twice with EtOAc (30mL). the combined organic phases were washed with brine (30mL), dried with Na_2SO_4, and concentrated. The residue was purified using a silica gel column eluted with PE/EtOAc (15:1) to afford the product (41 mg, 60%).

18h was prepared according to general procedure with 1-(2-chloro-1-methoxy-4,5,6a,7-tetrahydro-6H-dibenzo[de,g]quinolin-6-yl)-2,2,2-trifl uoroethan-1-one (41 mg, 0.11 mmol) as a white solid (18 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.84 (s, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.32 (m, 4H), 4.32 (d, *J* = 10.6 Hz, 1H), 3.65 – 3.56 (m, 4H), 3.25 – 3.19 (m, 2H), 3.14 (dd, *J* = 14.0, 4.1 Hz, 1H), 3.07 – 2.92 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 151.9, 134.1, 130.7, 130.6, 129.8, 129.2, 129.0, 128.9, 128.4, 128.3, 128.0, 127.7, 60.5, 52.1, 32.6, 24.7. HRMS (CI) calcd for $C_{17}H_{17}ClNO$ $[M+H]^+$: 286.0999, found 286.0987.

2-Bromo-1-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**18i**)

BBr_3 (1 M in DCM, 2.0 eq) was added dropwise to a solution of **17b** (1.0 eq) in DCM (0.2 M) at -78 ℃ under nitrogen atmosphere. The reaction mixture was then allowed to warm to room temperature for 1 h. The reaction was quenched with ice cold water, extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was obtained as a white solid and used directly for the next step without further purification. Bromine (1.2 eq) was added at 0 ℃ to a solution of crude product in HOAc (0.2M) and stirred at room temperature for 1 h. The dark red solution was discoloured with sodium thiosulfate solution (1M), washed with water (20 mL) and separated. The aqueous layer was extracted into DCM (25 mL × 2) and the combined organic layers dried over Na_2SO_4, filtered and evaporated. The residue was purified using a silica gel column eluted with PE/EtOAc (20:1) to afford the product 1-(2-bromo-1-hydroxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[de,g]quinolin-6-yl)-2,2,2-trifl uoroethan-1-one.

A solution of above product (85 mg, 1.62 mmol), MeI (0.02 mL, 0.31 mmol), and K_2CO_3 (43mg, 0.31 mmol) in Acetone (3 mL) was refluxed for 4 h. The reaction mixture was diluted with DCM and water. The aqueous layer was extracted with DCM (20 mL × 3), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using PE/EtOAc (30:1) as eluant to give 1-(2-bromo-1-methoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[de,g]quinolin-6-yl)-2,2,2-trifl

uoroethan-1-one as a white solid (55 mg, 63%).

18i was prepared according to general procedure with 1-(2-bromo-1-methoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[de,g]quinolin-6-yl)-2,2,2-trifluoroethan-1-one (50 mg, 0.11 mmol) as a white solid (25 mg, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.09 (s, 2H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.59 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.32 (m, 1H), 4.29 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.58 (d, *J* = 6.4 Hz, 1H), 3.52 (s, 3H), 3.26 – 3.20 (m, 2H), 3.13 (dd, *J* = 14.0, 4.2 Hz, 1H), 3.07 – 2.92 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.9, 134.2, 132.9, 131.5, 130.8, 129.6, 129.2, 128.9, 128.4, 127.9, 127.6, 118.4, 60.5, 52.2, 32.6, 24.7. HRMS (CI) calcd for $C_{17}H_{17}BrNO$ $[M+H]^+$: 330.0494, found 330.0488.

Asymmetric Synthesis of Compounds (*S*)-18b and (*R*)-18b

(R)-1-(2-bromobenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**(*R*)-13b**)

19b (280 mg, 0.85 mmol) was dissolved in 2 mL of DMF, and RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) (18 mg, 0.03 mmol)was added (S/C = 30). A total of 1 mL (molar ratio = 5:2) of azeotrope of HCOOH and TEA was added under ice bath, and the mixture was gradually warmed to room temperature and stirred for 12 h. The DMF was removed, and the product was extracted with DCM (30 mL× 2), washed with brine and dried. The residue was purified by column chromatography on silica gel using DCM/MeOH/NH_4OH (50:1:0.5) as eluant to give **(*R*)-13b** (160 mg, 57%) as a pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 4.2 Hz, 2H), 7.16 – 7.11 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 6.76 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.31 (d, *J* = 9.8 Hz, 1H), 3.79 (s, 3H), 3.41 (dd, *J* = 13.7, 3.1 Hz, 1H), 3.28 – 3.22 (m, 1H), 3.03 – 2.94 (m, 2H), 2.82 – 2.73 (m, 2H), 1.83 (s, 1H).

(S)-1-(2-bromobenzyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**(*S*)-13b**)

Compound **12b** (1.0 eq) and P_2O_5 (5.0 eq) were refluxed in toluene for 3 h, and a white precipitate was precipitated from the solution. Then, toluene was evaporated, and the solid was treated with saturated aqueous $NaHCO_3$ and EtOAc. The extract was separated and the organic phase was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 50:1) to the desired product **19b** as a yellow oil. **19b** (280 mg, 0.85 mmol) was dissolved in 2 mL of anhydrous DMF, and RuCl[(*R*,*R*)-TsDPEN](*p*-cymene) (18 mg, 0.03 mmol)

was added (S/C = 30). A total of 1 mL (molar ratio = 5:2) of azeotrope of HCOOH and TEA was added under ice bath, and the mixture was gradually warmed to room temperature and stirred for 12 h. The DMF was removed, and the product was extracted with anhydrous DCM (30 mL × 2), washed with brine and dried. The residue was purified by column chromatography on silica gel using DCM/MeOH/NH_4OH (50:1:0.5) as the eluent to give **(*S*)-13b** (160 mg, 57%) as a pale green oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 4.2 Hz, 2H), 7.16 – 7.11 (m, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 1H), 6.76 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.31 (d, *J* = 9.8 Hz, 1H), 3.79 (s, 3H), 3.41 (dd, *J* = 13.7, 3.1 Hz, 1H), 3.28 – 3.22 (m, 1H), 3.03 – 2.94 (m, 2H), 2.82 – 2.73 (m, 2H), 1.83 (s, 1H).

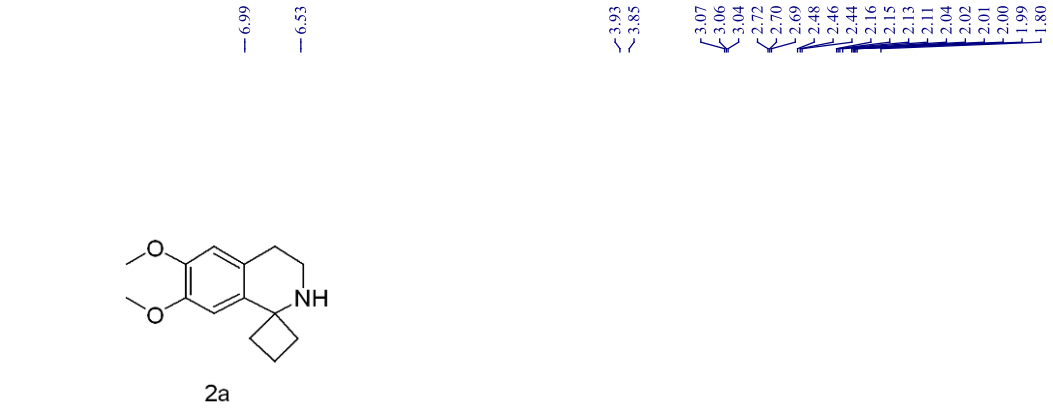
(R)-1-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolone hydrochloride (**(*R*)-18b**)

The **(*R*)-18b** was prepared in the same manner as described in synthesis of **18b** starting from **(*R*)-13b** (30% for three-step, 94% ee, t_R = 14 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 9.54 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.77 – 7.22 (m, 4H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.35 – 4.25 (m, 1H), 3.86 (s, 3H), 3.62 – 3.56 (m, 1H), 3.25 – 3.16 (m, 2H), 3.09 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.99 – 2.91 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6, 133.6, 131.7, 131.2, 129.7, 129.0, 128.4, 127.9, 127.5, 123.3, 121.2, 113.1, 56.4, 52.6, 33.0, 24.7. HRMS (CI) calcd for $C_{17}H_{19}ClNO$ $[M+H]^+$: 252.1388, found 252.1381. α_D^{25} = - 92.00 (*c* = 1, MeOH).

(S)-1-methoxy-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolone hydrochloride (**(*S*)-18b**)

The **(*S*)-18b** was prepared in the same manner as described in synthesis of **18b** starting from **(*S*)-13b** (30% for three-step, 96% ee, t_R = 16 min). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (d, *J* = 6.5 Hz, 1H), 9.76 (d, *J* = 7.5 Hz, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.28 – 7.19 (m, 2H), 7.15 (d, *J* = 8.6 Hz, 1H), 4.32 – 4.26 (m, 1H), 3.85 (s, 3H), 3.56 (d, *J* = 5.9 Hz, 1H), 3.22 – 3.19 (m, 2H), 3.11 (dd, *J* = 13.8, 4.2 Hz, 1H), 3.03 – 2.85 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.6, 133.6, 131.7, 131.1, 129.6, 128.9, 128.3, 127.8, 127.4, 123.4, 121.2, 113.2, 56.4, 52.6, 40.6, 33.0, 24.7. HRMS (CI) calcd for $C_{17}H_{19}ClNO$ $[M+H]^+$: 252.1388, found 252.1383. α_D^{25} = + 92.86 (*c* = 1, MeOH).

^{1}H and ^{13}C NMR Spectra



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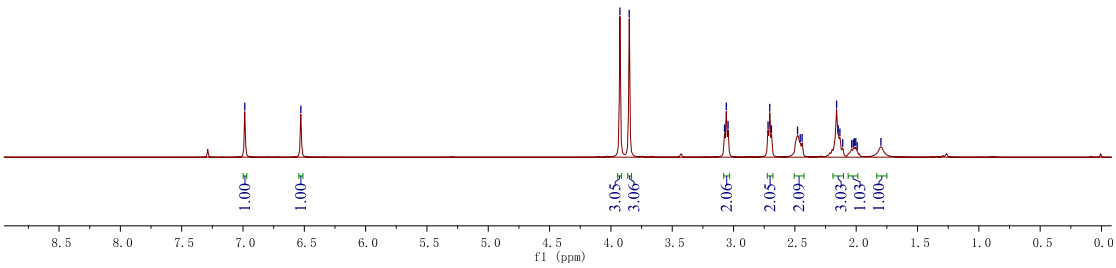

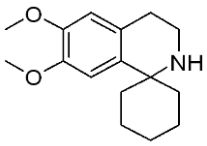

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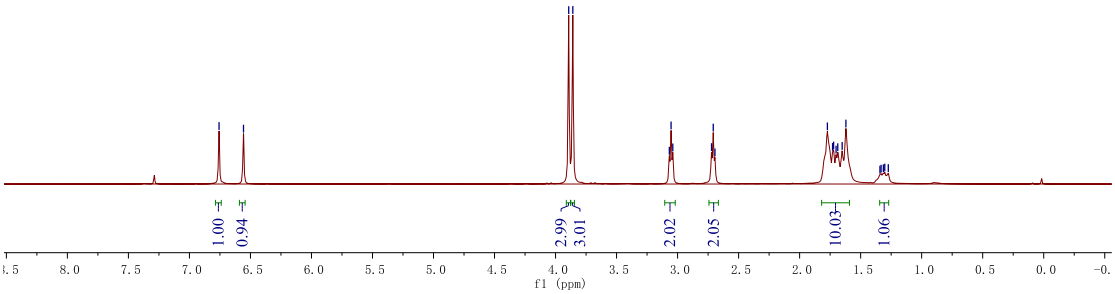

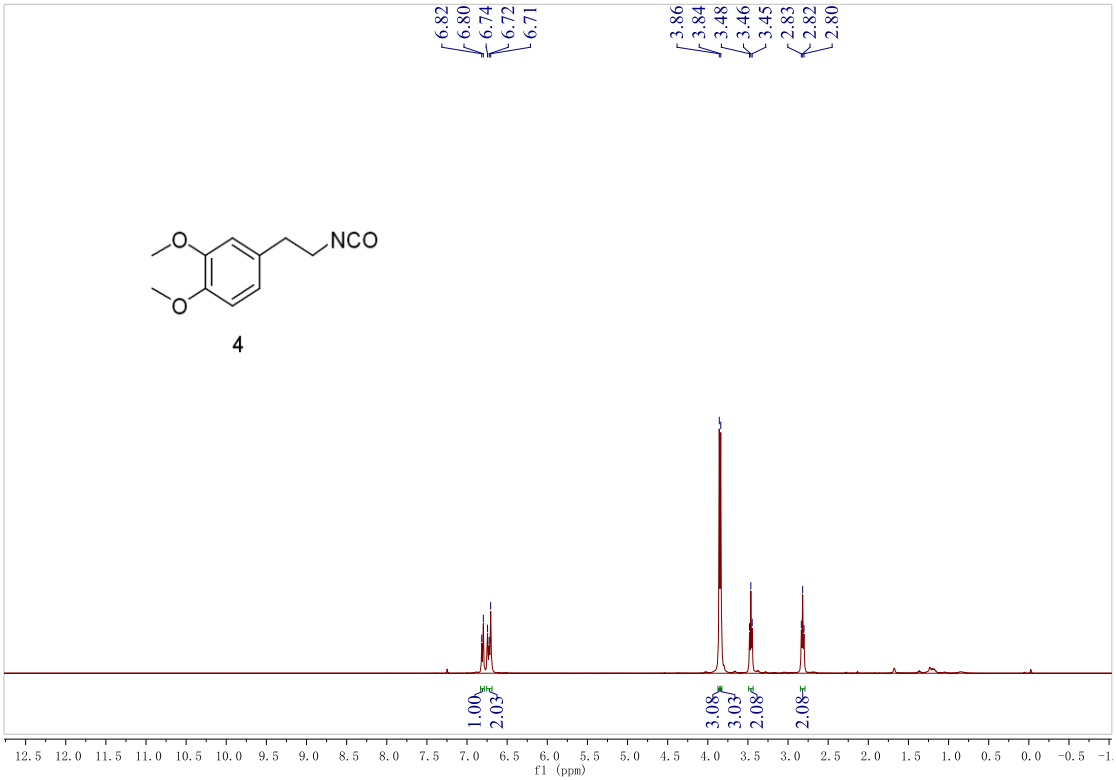
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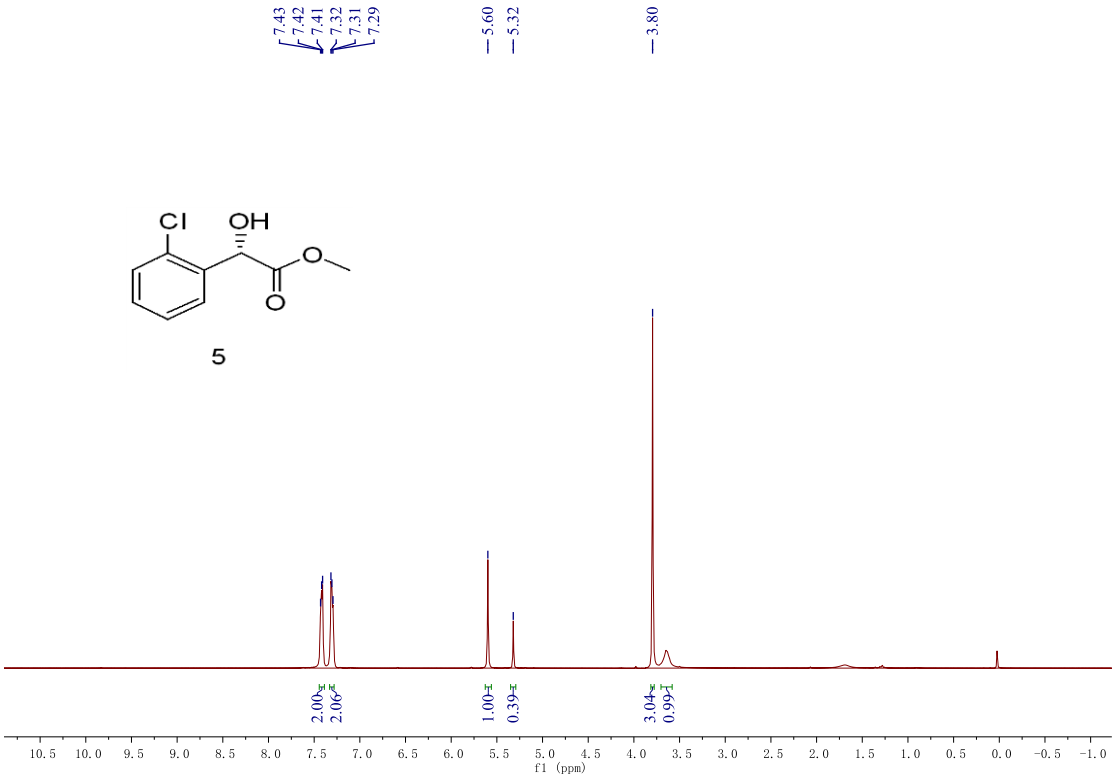
4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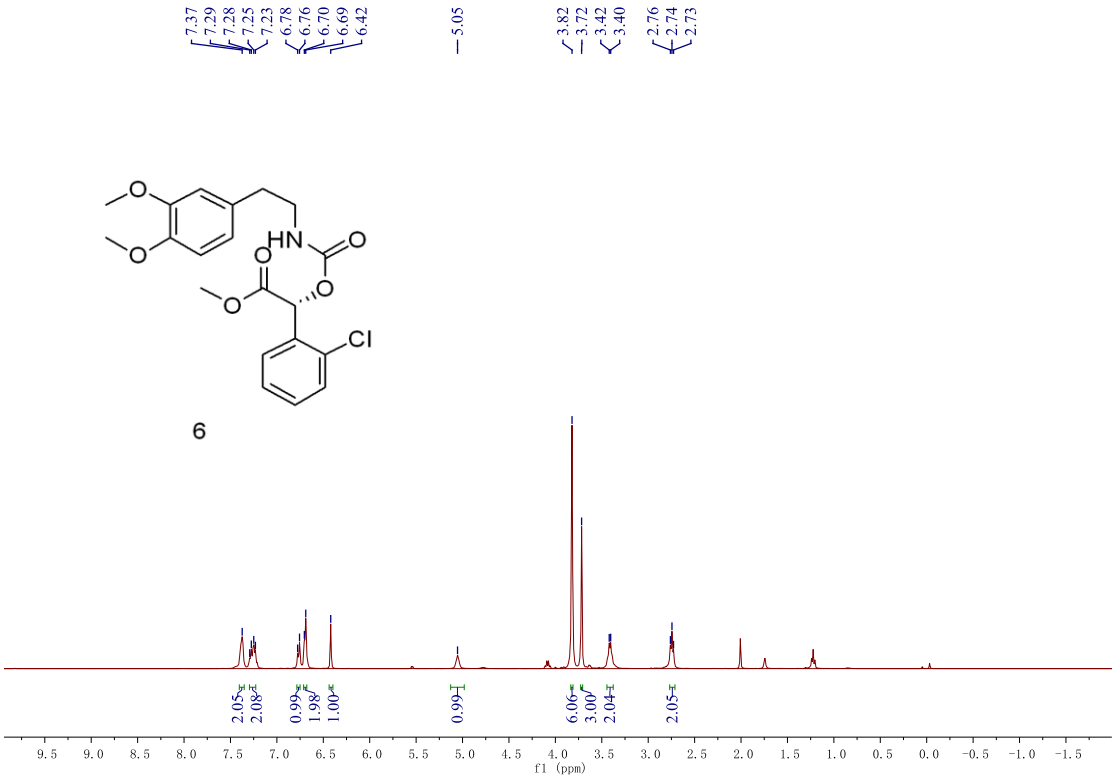
f1 (ppm)

5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7.28
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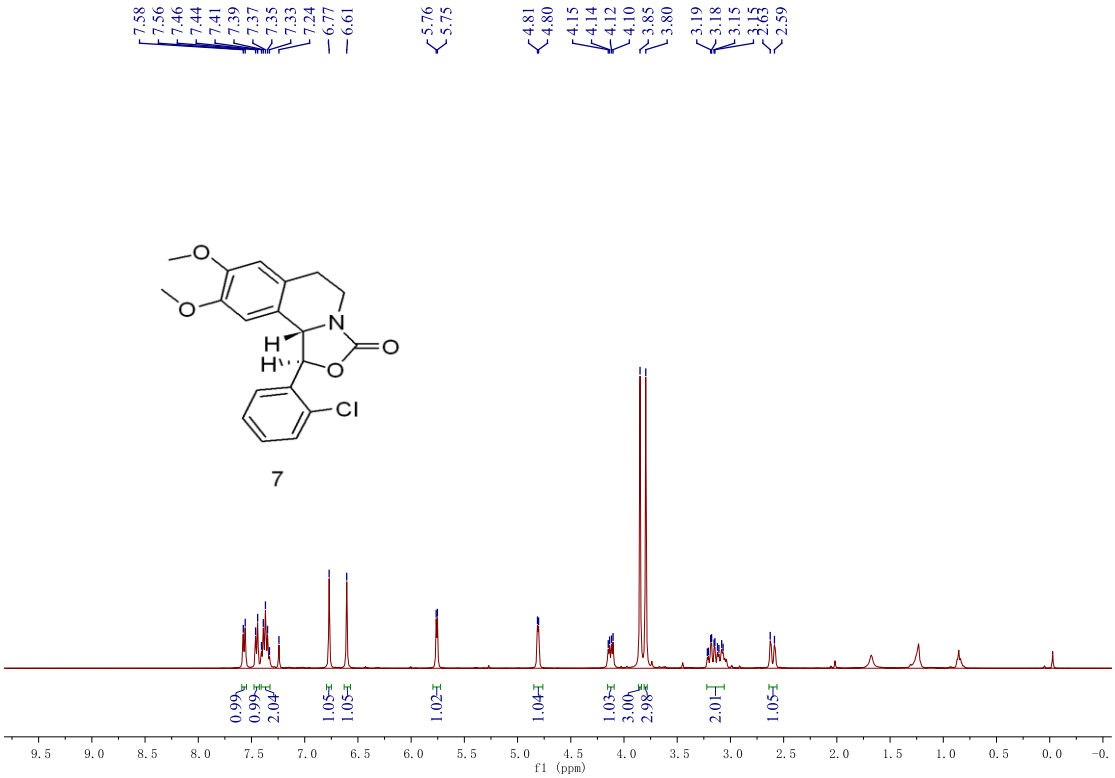
6.78
6.76
6.70
6.69
6.42
5.05
3.82
3.72
3.42
3.40
2.76
2.74
2.73
HN
O
O
O
O
O
O
Cl
2.05
2.08
0.99
1.98
1.00
0.99
6.06
3.00
2.04
2.05
f1 (ppm)

6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7.56
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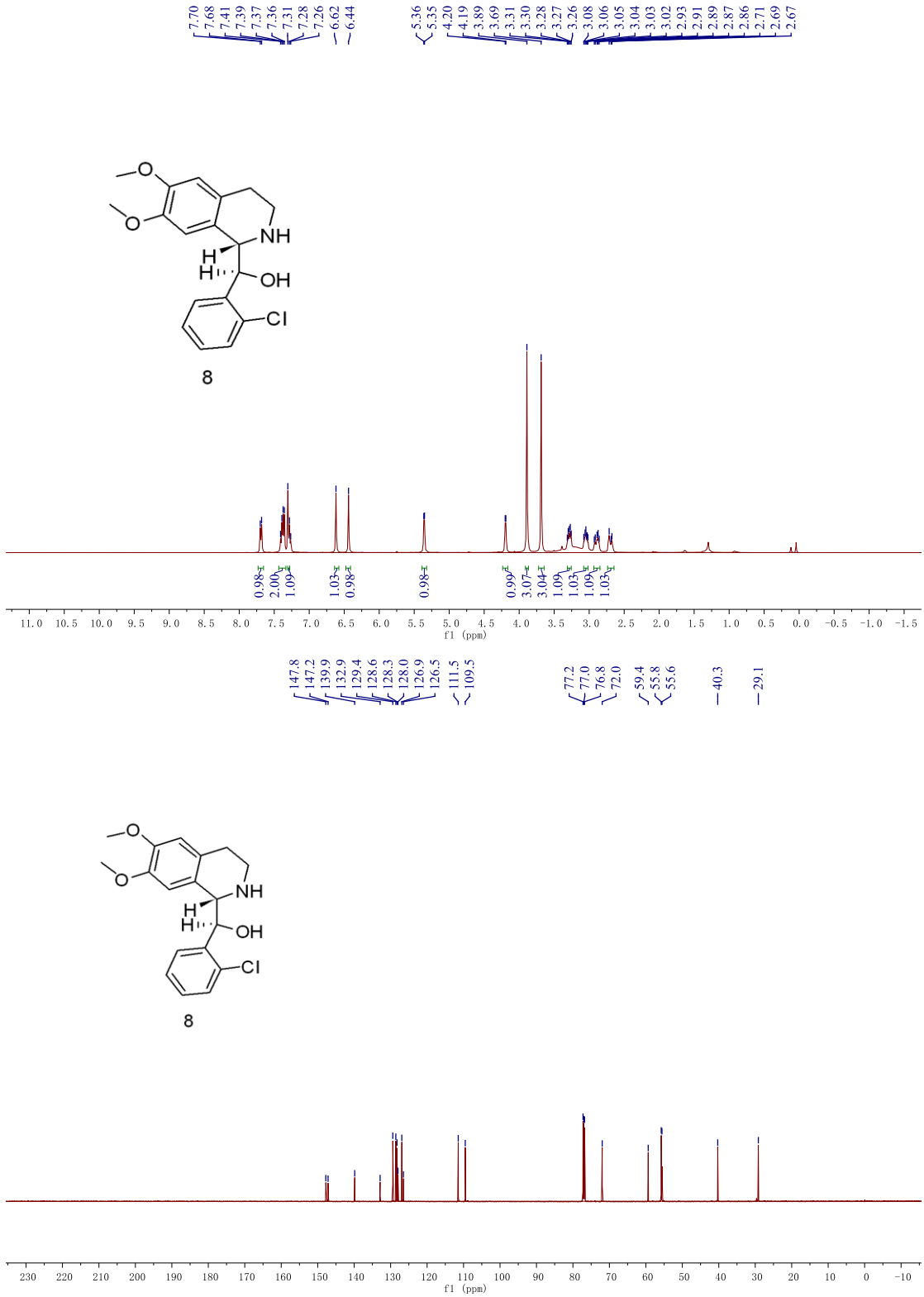
7.41
7.39
7.37
7.35
7.33
7.24
6.77
6.61
5.76
5.75
4.81
4.80
4.15
4.14
4.12
4.10
3.85
3.80
3.19
3.18
3.15
3.15
2.63
2.59
O
O
N
H
H
O
O
Cl
0.99
0.99
2.04
1.05
1.05
1.02
1.04
1.03
3.00
2.98
2.01
1.05
f1 (ppm)

7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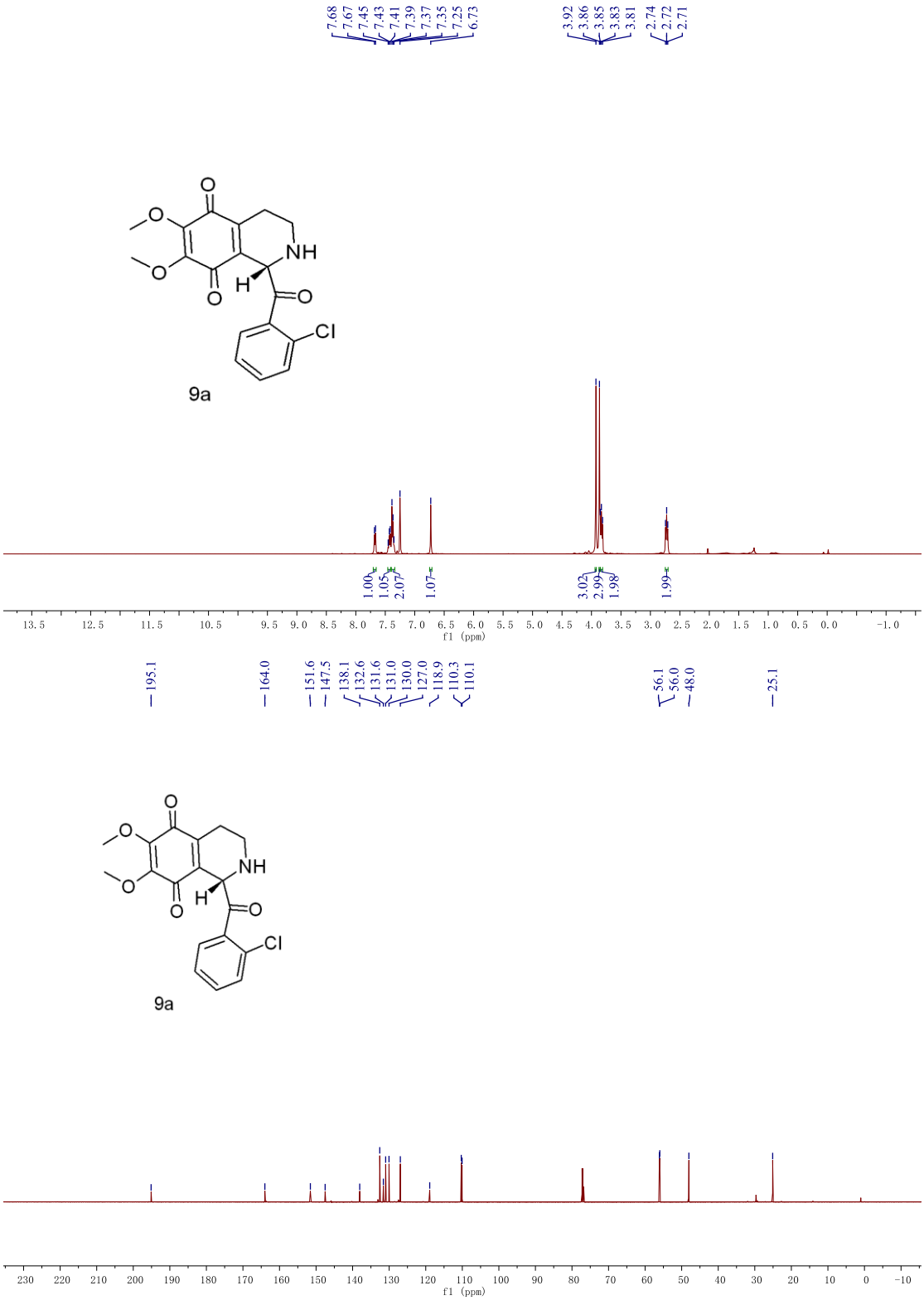
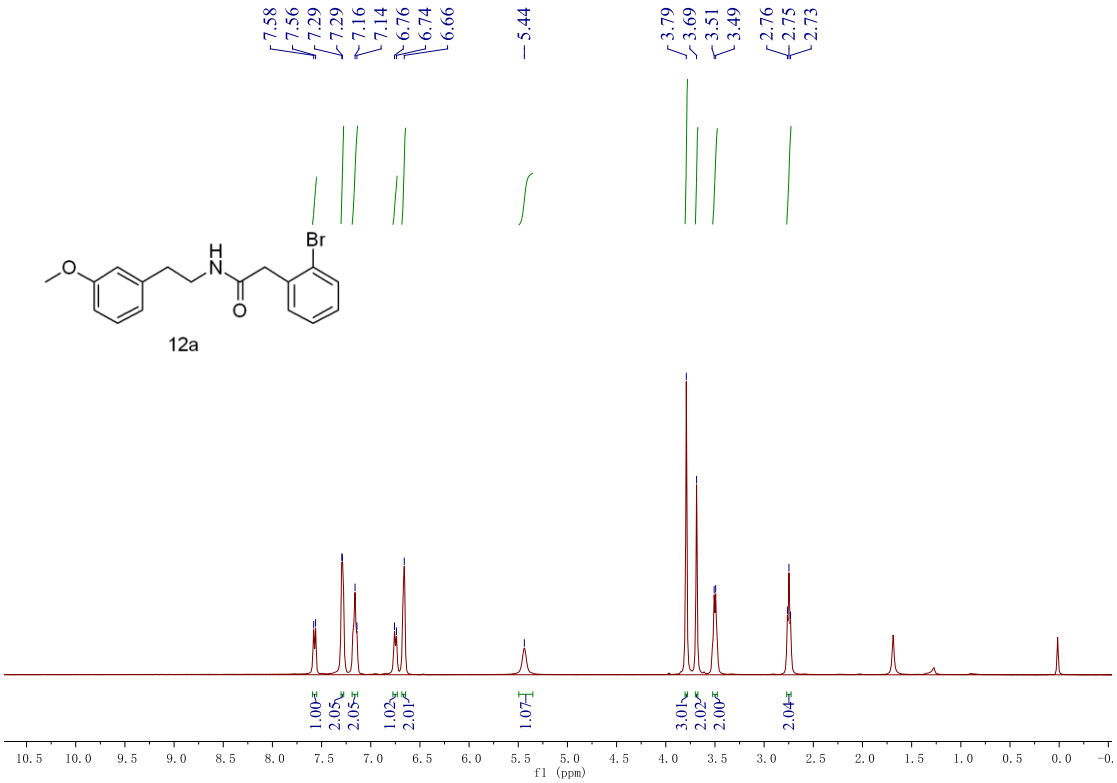
7.28
7.26
6.62
6.44
5.36
5.35
4.20
4.19
3.89
3.69
3.31
3.30
3.28
3.27
3.26
3.08
3.06
3.05
3.04
3.03
3.02
2.93
2.91
2.89
2.87
2.86
2.71
2.69
2.67
O
O
NH
H
H
OH
Cl
8
0.98
2.00
1.09
1.03
0.98
0.98
0.99
3.07
3.04
1.09
1.03
1.09
1.03
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)
147.8
147.2
139.9
132.9
129.4
128.6
128.3
128.0
126.9
126.5
111.5
109.5
77.2
77.0
76.8
72.0
59.4
55.8
55.6
40.3
29.1
O
O
NH
H
H
OH
Cl
8
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.68
7.67
7.45
7.43
7.41
7.39
7.37
7.35
7.25
6.73
3.92
3.86
3.85
3.83
3.81
2.74
2.72
2.71
O
O
O
O
NH
H
O
Cl
9a
1.00
1.05
2.07
1.07
3.02
2.99
1.98
1.99
f1 (ppm)
195.1
164.0
151.6
147.5
138.1
132.6
131.6
131.0
130.0
127.0
118.9
110.3
110.1
56.1
56.0
48.0
25.1
f1 (ppm)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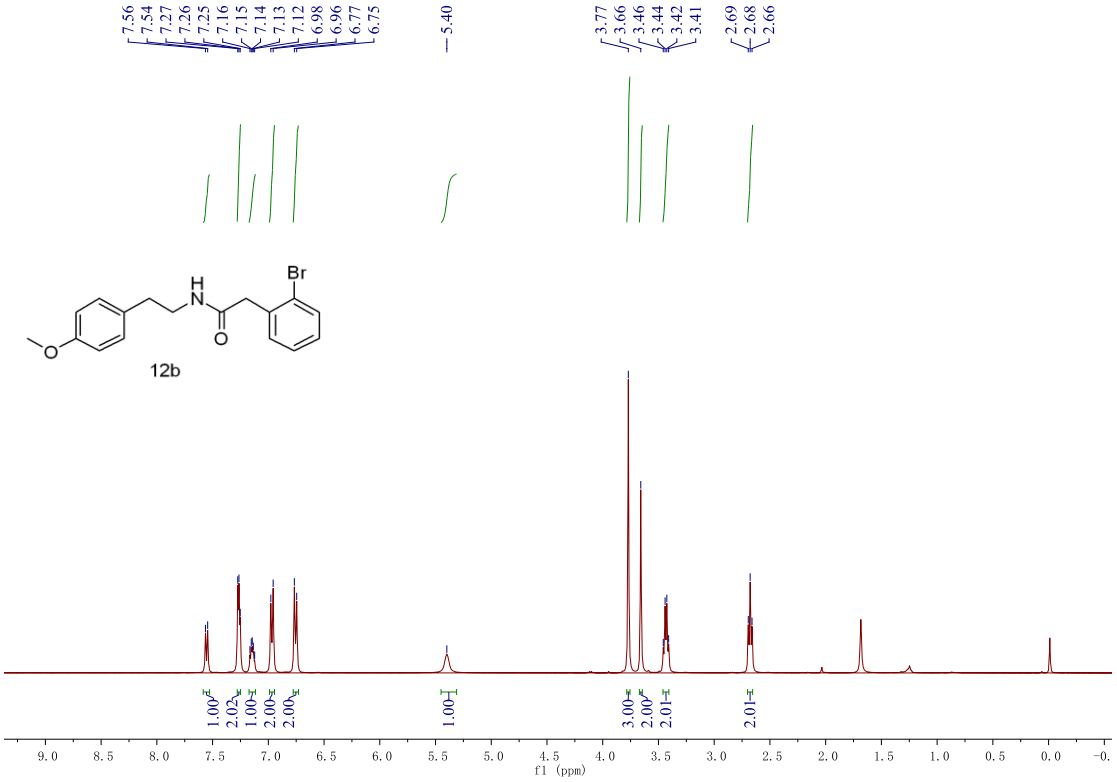
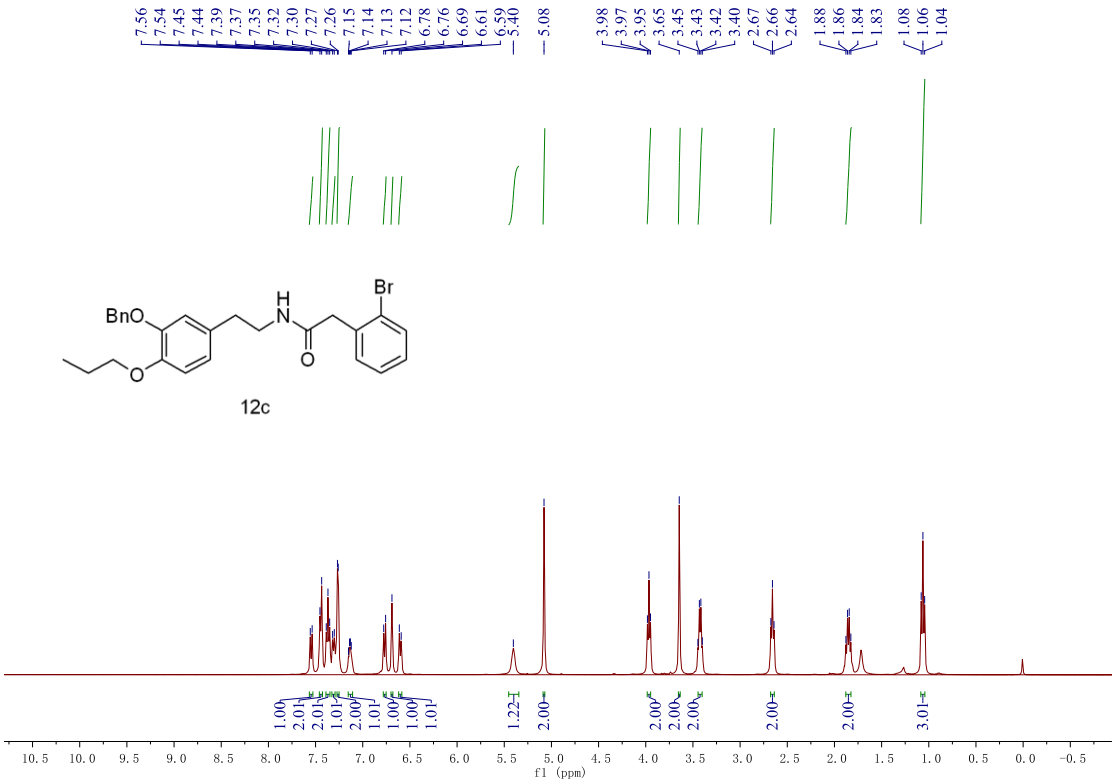
7.56
7.29
7.29
7.16
7.14
6.76
6.74
6.66
5.44
3.79
3.69
3.51
3.49
2.76
2.75
2.73
Br
H
N
O
O
12a
1.00
2.05
2.05
1.02
2.01
1.07
3.01
2.02
2.00
2.04
f1 (ppm)


7.56
7.54
7.27
7.26
7.25
7.16
7.15
7.14
7.13
7.12
6.98
6.96
6.77
6.75
5.40
3.77
3.66
3.46
3.44
3.42
3.41
2.69
2.68
2.66
Br
H
N
O
O
12b
1.00
2.02
1.00
2.00
2.00
1.00
3.00
2.00
2.01
2.01
f1 (ppm)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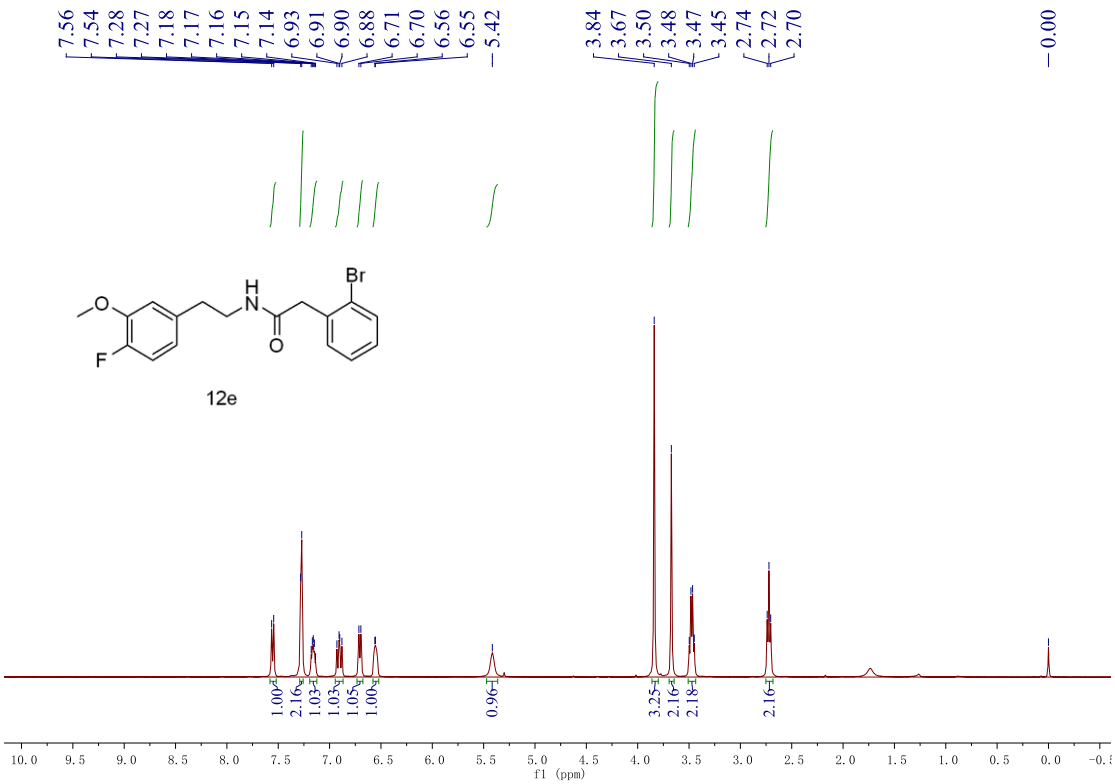
3.98 3.97 3.95 3.65 3.45 3.43 3.42 3.40 2.67 2.66 2.64 1.88 1.86 1.84 1.83 1.08 1.06 1.04
BnO
H
N
O
Br
O
12c
1.00 2.01 1.01 1.01 2.00 1.01 1.00 1.00 1.01 1.22 2.00 2.00 2.00 2.00 2.00 2.00 3.01
f1 (ppm)
7.55 7.53 7.46 7.44 7.38 7.37 7.35 7.32 7.30 7.26 7.15 7.14 7.13 7.12 7.11 6.78 6.76 6.68 6.60 6.58 5.36 5.09
3.85 3.84 3.64 3.44 3.42 3.41 3.39 2.66 2.65 2.63 1.31 1.29 1.27 0.63 0.61 0.35 0.34 0.00
BnO
H
N
O
Br
O
12d
1.00 2.04 2.04 1.01 2.01 1.08 1.08 1.06 1.03 1.07 2.09 2.11 2.05 2.11 2.17 1.10 2.16 2.05
f1 (ppm)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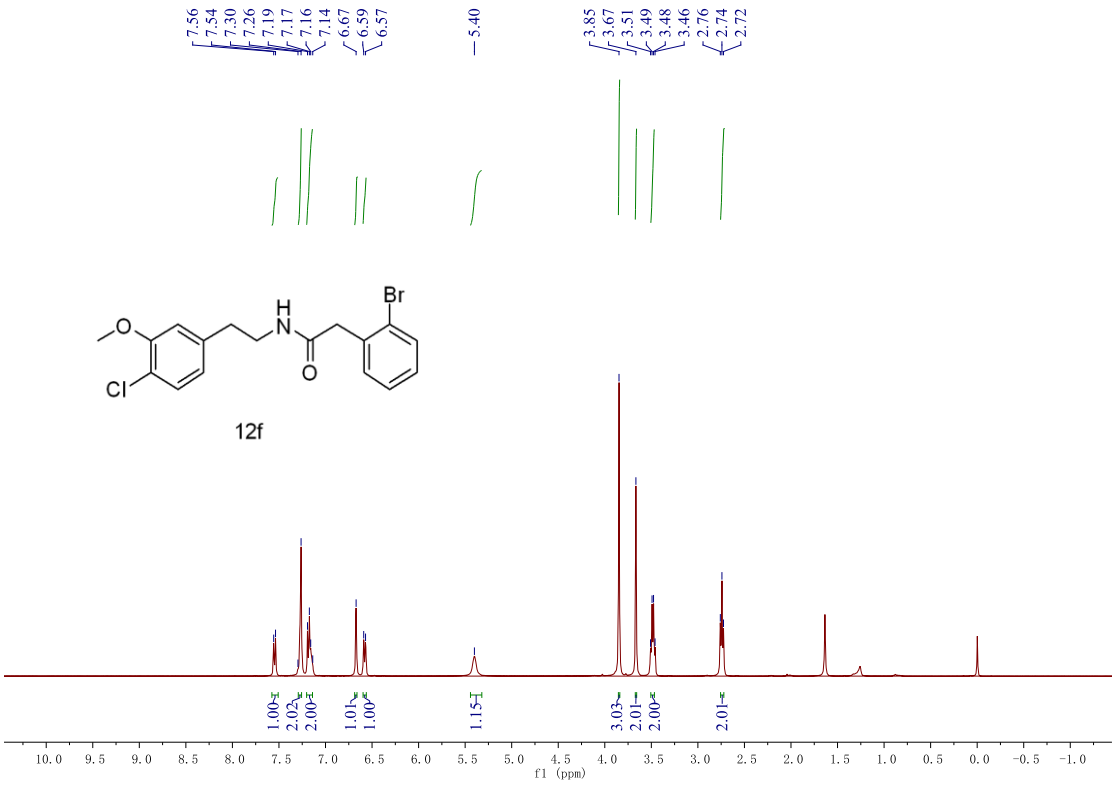
7.28
7.27
7.18
7.17
7.16
7.15
7.14
6.93
6.91
6.90
6.88
6.71
6.70
6.56
6.55
5.42
3.84
3.67
3.50
3.48
3.47
3.45
2.74
2.72
2.70
0.00
Br
O
H
N
O
F
1.00
2.16
1.03
1.03
1.05
1.00
0.96
3.25
2.16
2.18
2.16
f1 (ppm)

12e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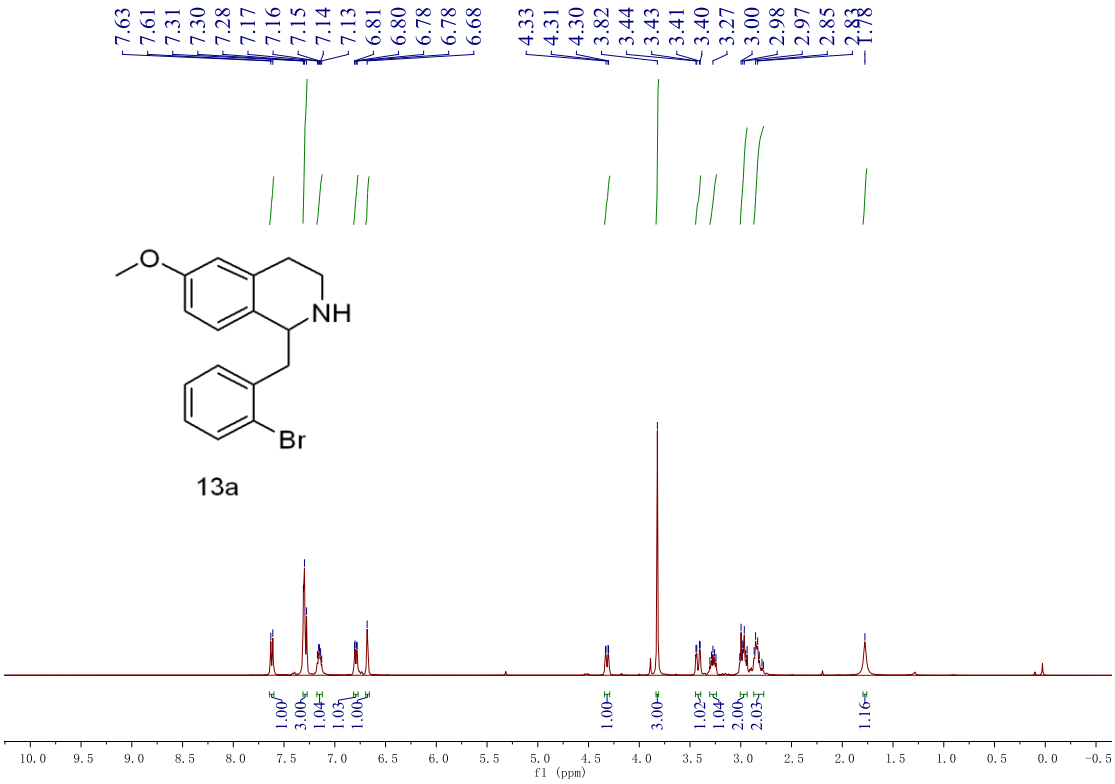
7.54
7.30
7.26
7.19
7.17
7.16
7.14
6.67
6.59
6.57
5.40
3.85
3.67
3.51
3.49
3.48
3.46
2.76
2.74
2.72
Br
O
H
N
O
Cl
1.00
2.02
2.00
1.01
1.00
1.15
3.03
2.01
2.00
2.01
f1 (ppm)

12f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7.31
7.30
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7.17
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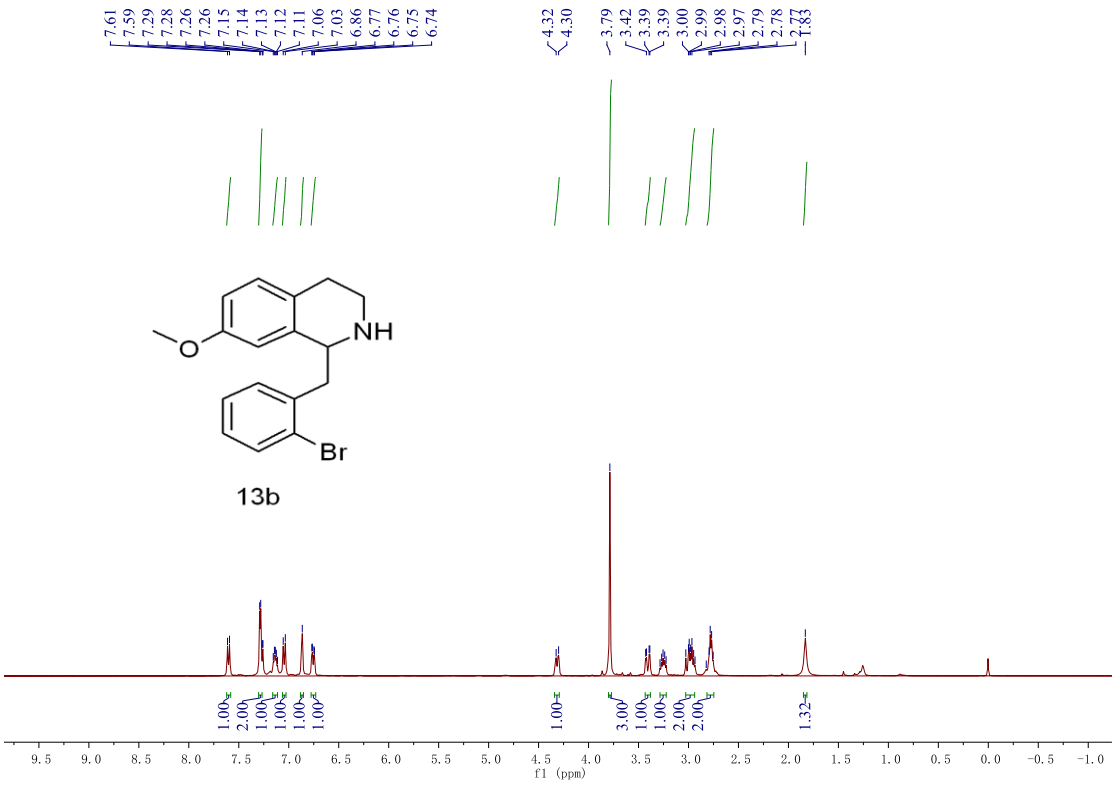
7.15
7.14
7.13
6.81
6.80
6.78
6.78
6.68
4.33
4.31
4.30
3.82
3.44
3.43
3.41
3.40
3.27
3.00
2.98
2.97
2.85
2.83
1.78
O
NH
Br
1.00
3.00
1.04
1.03
1.00
1.00
3.00
1.02
1.04
2.00
2.03
1.16
f1 (ppm)

13a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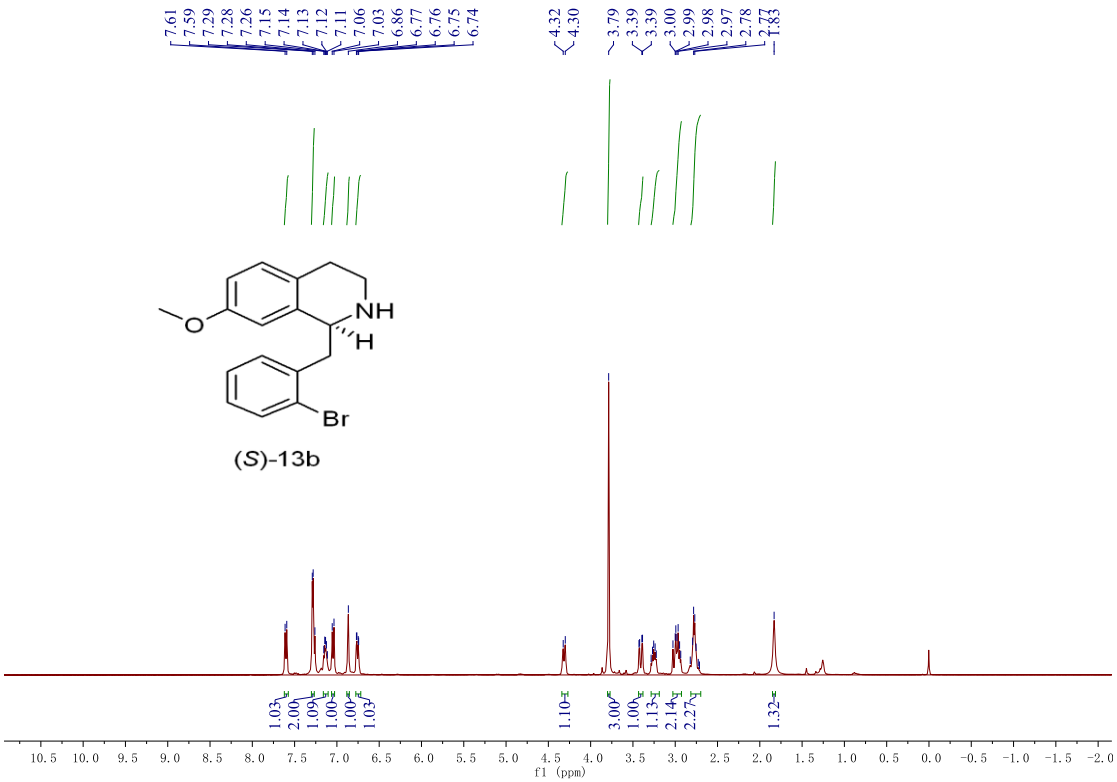
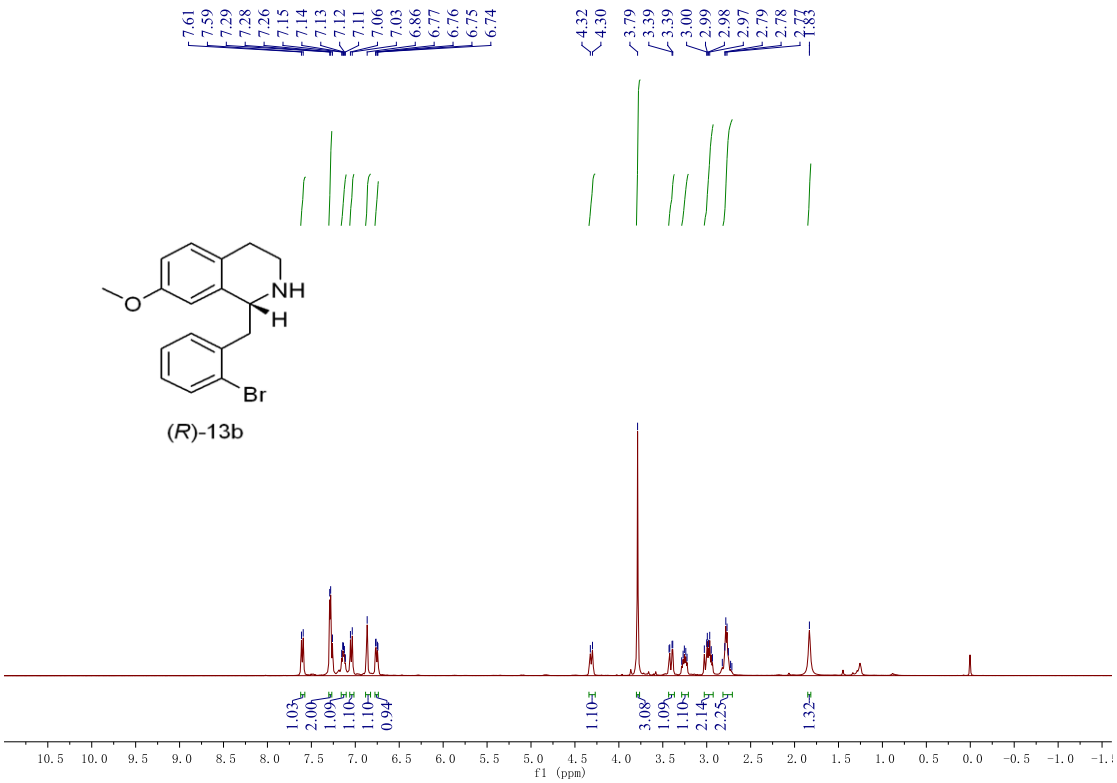
7.59
7.29
7.28
7.26
7.26
7.15
7.14
7.13
7.12
7.11
7.06
7.03
6.86
6.77
6.76
6.75
6.74
4.32
4.30
3.79
3.42
3.39
3.39
3.00
2.99
2.98
2.97
2.79
2.78
2.77
1.83
NH
O
Br
1.00
2.00
1.00
1.00
1.00
1.00
1.00
3.00
1.00
1.00
2.00
2.00
1.32
f1 (ppm)

13b


7.61
7.59
7.29
7.28
7.26
7.15
7.14
7.13
7.12
7.11
7.06
7.03
6.86
6.77
6.76
6.75
6.74
4.32
4.30
3.79
3.39
3.39
3.00
2.99
2.98
2.97
2.78
1.83
NH
H
O
Br
1.03
2.00
1.09
1.00
1.00
1.03
1.10
3.00
1.00
1.13
2.14
2.27
1.32
f1 (ppm)

(*S*)-13b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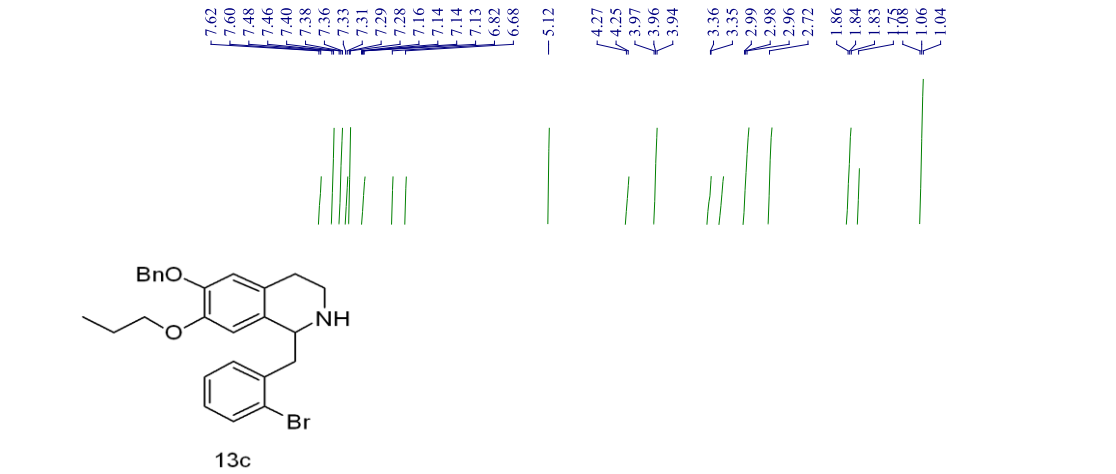
7.59
7.29
7.28
7.26
7.15
7.14
7.13
7.12
7.11
7.06
7.03
6.86
6.77
6.76
6.75
6.74
4.32
4.30
3.79
3.39
3.39
3.00
2.99
2.98
2.97
2.79
2.78
1.83
NH
H
O
Br
1.03
2.00
1.09
1.10
1.10
0.94
1.10
3.08
1.09
1.10
2.14
2.25
1.32
f1 (ppm)

(*R*)-13b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7.60
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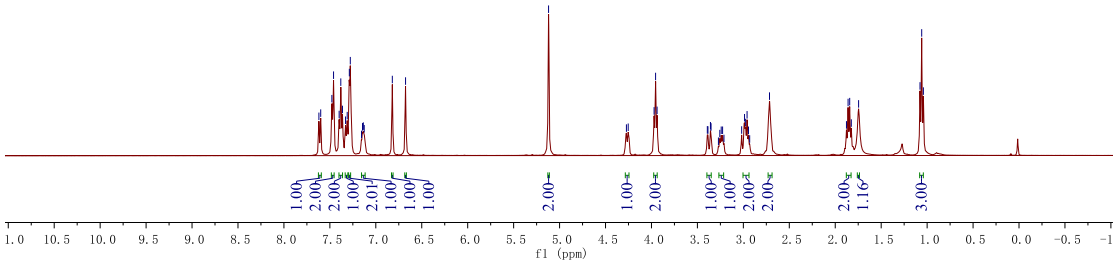
7.46
7.40
7.38
7.36
7.33
7.31
7.29
7.28
7.16
7.14
7.14
7.13
6.82
6.68
5.12
4.27
4.25
3.97
3.96
3.94
3.36
3.35
2.99
2.98
2.96
2.72
1.86
1.84
1.83
1.08
1.06
1.04
BnO
O
NH
Br

13c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2.00
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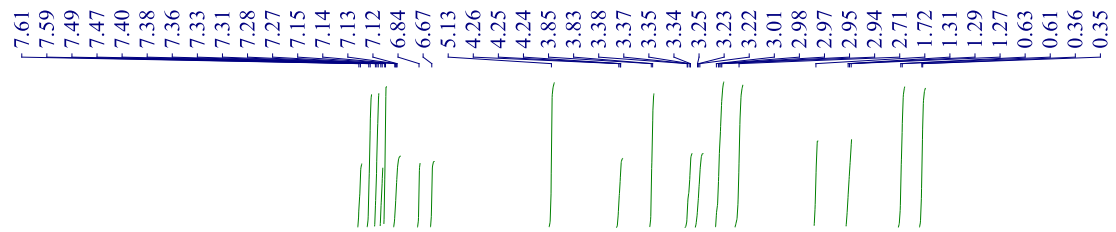
1.00
2.01
1.00
1.00
1.00
2.00
1.00
2.00
1.00
1.00
2.00
2.00
1.16
3.00
f1 (ppm)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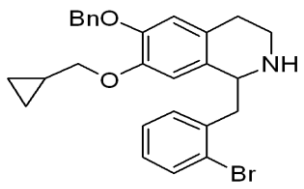
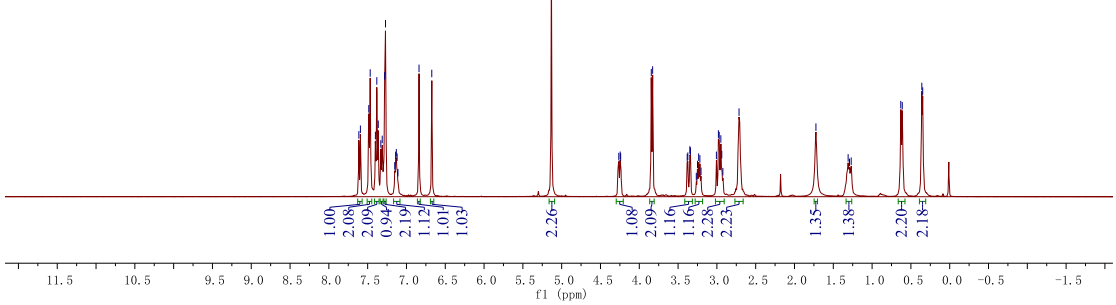
7.47
7.40
7.38
7.36
7.33
7.31
7.28
7.27
7.15
7.14
7.13
7.12
6.84
6.67
5.13
4.26
4.25
4.24
3.85
3.83
3.38
3.37
3.35
3.34
3.25
3.23
3.22
3.01
2.98
2.97
2.95
2.94
2.71
1.72
1.31
1.29
1.27
0.63
0.61
0.36
0.35


BnO
O
NH
Br

13d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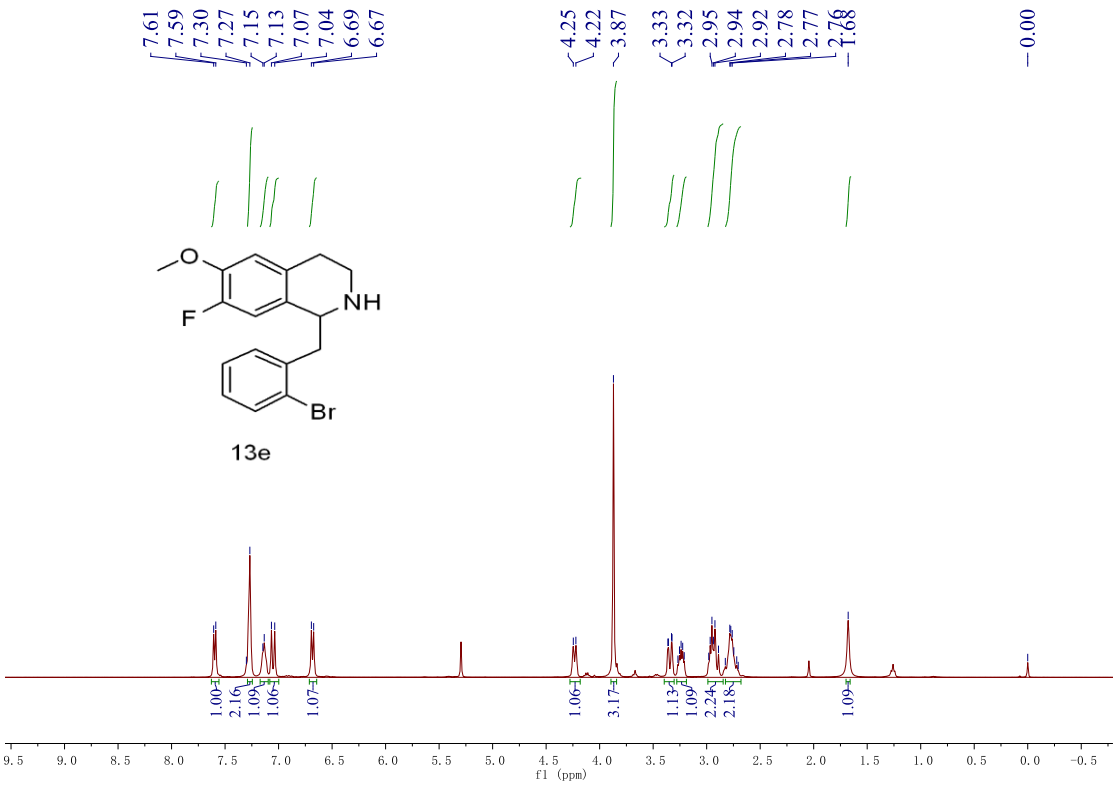
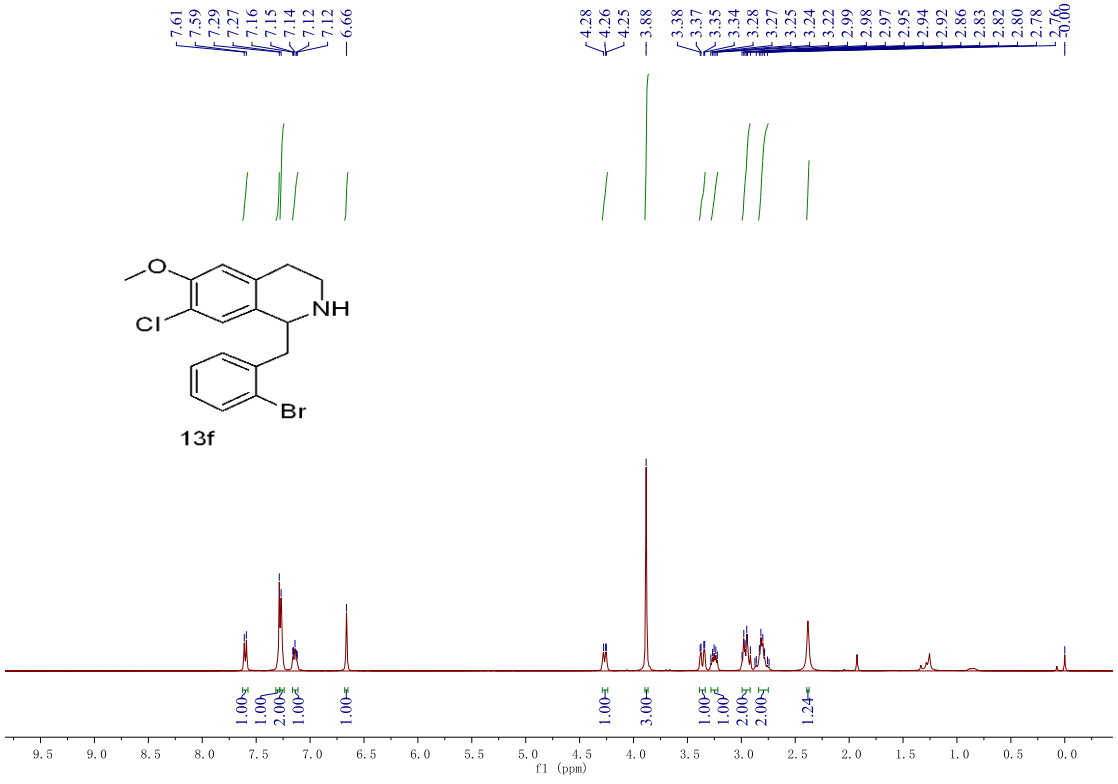
2.08
2.09
0.94
2.19
1.12
1.01
1.03
2.26
1.08
2.09
1.16
1.16
2.28
2.23
1.35
1.38
2.20
2.18
f1 (ppm)


7.61
7.59
7.30
7.27
7.15
7.13
7.07
7.04
6.69
6.67
4.25
4.22
3.87
3.33
3.32
2.95
2.94
2.92
2.78
2.77
1.68
0.00
O
F
NH
Br
13e
1.00
2.16
1.09
1.06
1.07
1.06
3.17
1.13
1.09
2.24
2.18
1.09
f1 (ppm)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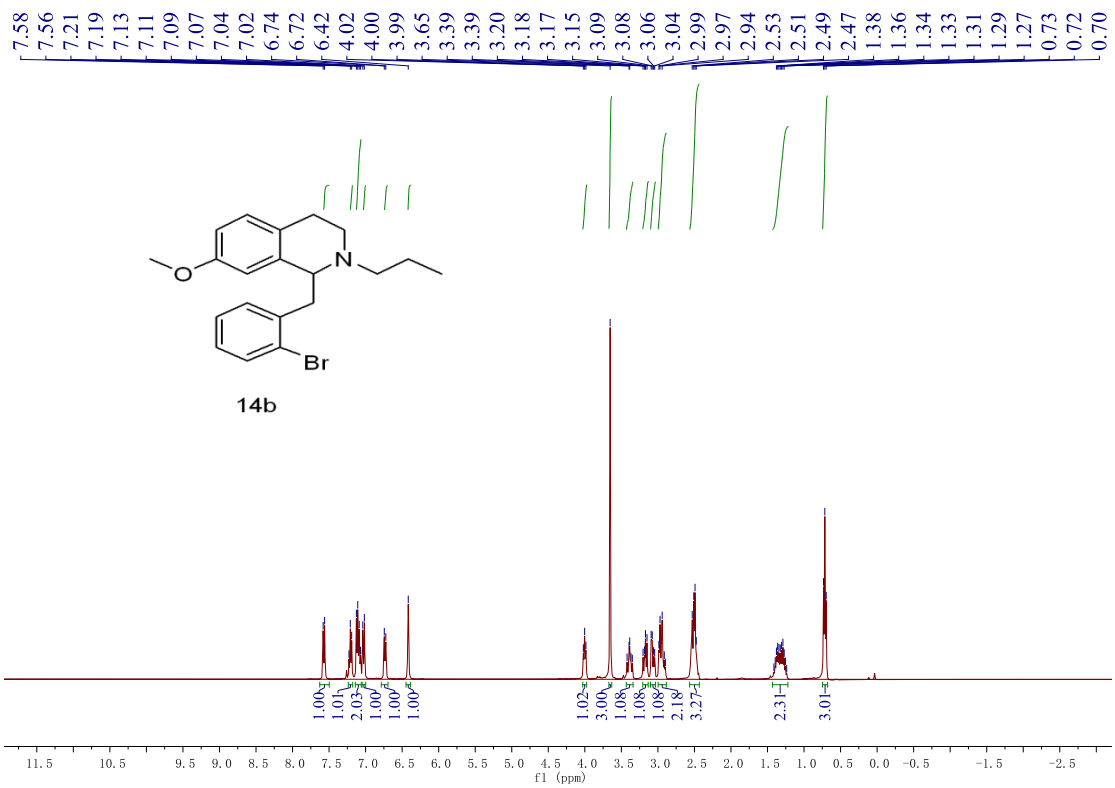
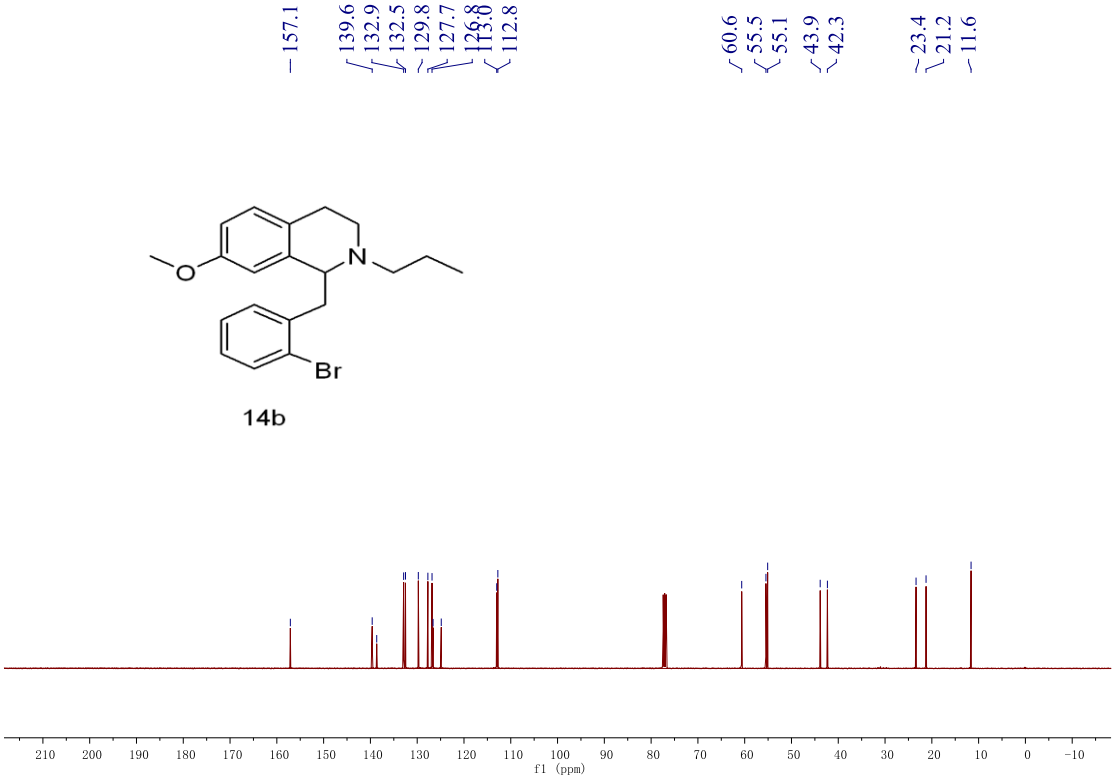
7.59
7.29
7.27
7.16
7.15
7.14
7.12
7.12
6.66
4.28
4.26
4.25
3.88
3.38
3.37
3.35
3.34
3.28
3.27
3.25
3.24
3.22
2.99
2.98
2.97
2.95
2.94
2.92
2.86
2.83
2.82
2.80
2.78
2.76
0.00
O
Cl
NH
Br
13f
1.00
1.00
2.00
1.00
1.00
1.00
3.00
1.00
1.00
2.00
2.00
1.24
f1 (ppm)

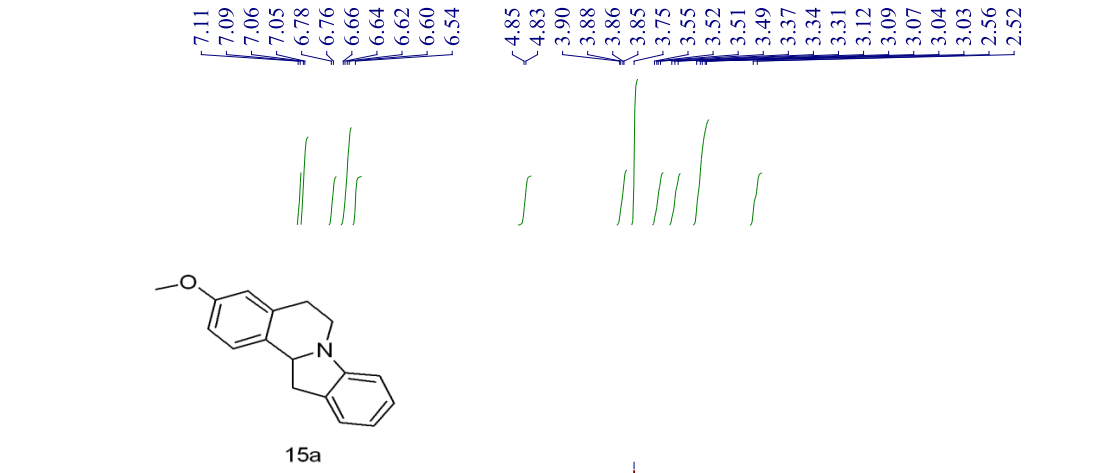

7.58
7.56
7.21
7.19
7.13
7.11
7.09
7.07
7.04
7.02
6.74
6.72
6.42
4.02
4.00
3.99
3.65
3.39
3.39
3.20
3.18
3.17
3.15
3.09
3.08
3.06
3.04
2.99
2.97
2.94
2.53
2.51
2.49
2.47
1.38
1.36
1.34
1.33
1.31
1.29
1.27
0.73
0.72
0.70
O
N
Br
1.00
1.01
2.03
1.00
1.00
1.00
1.02
3.00
1.08
1.08
1.08
2.18
3.27
2.31
3.01
f1 (ppm)

14b


157.1
139.6
132.9
132.5
129.8
127.7
126.8
113.0
112.8
60.6
55.5
55.1
43.9
42.3
23.4
21.2
11.6
f1 (ppm)

O
N
Br

14b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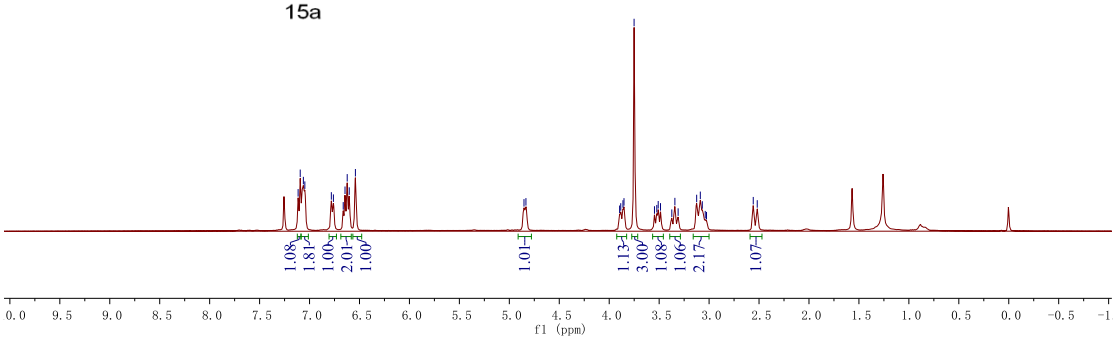
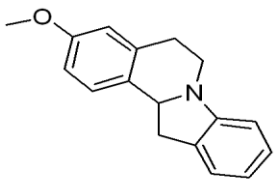
6.66
6.64
6.62
6.60
6.54
4.85
4.83
3.90
3.88
3.86
3.85
3.75
3.55
3.52
3.51
3.49
3.37
3.34
3.31
3.12
3.09
3.07
3.04
3.03
2.56
2.52
O
N

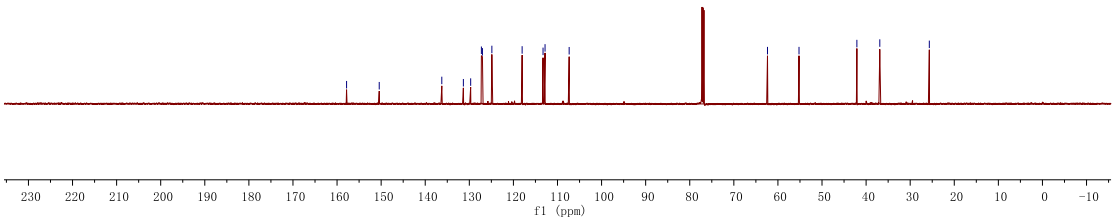
15a

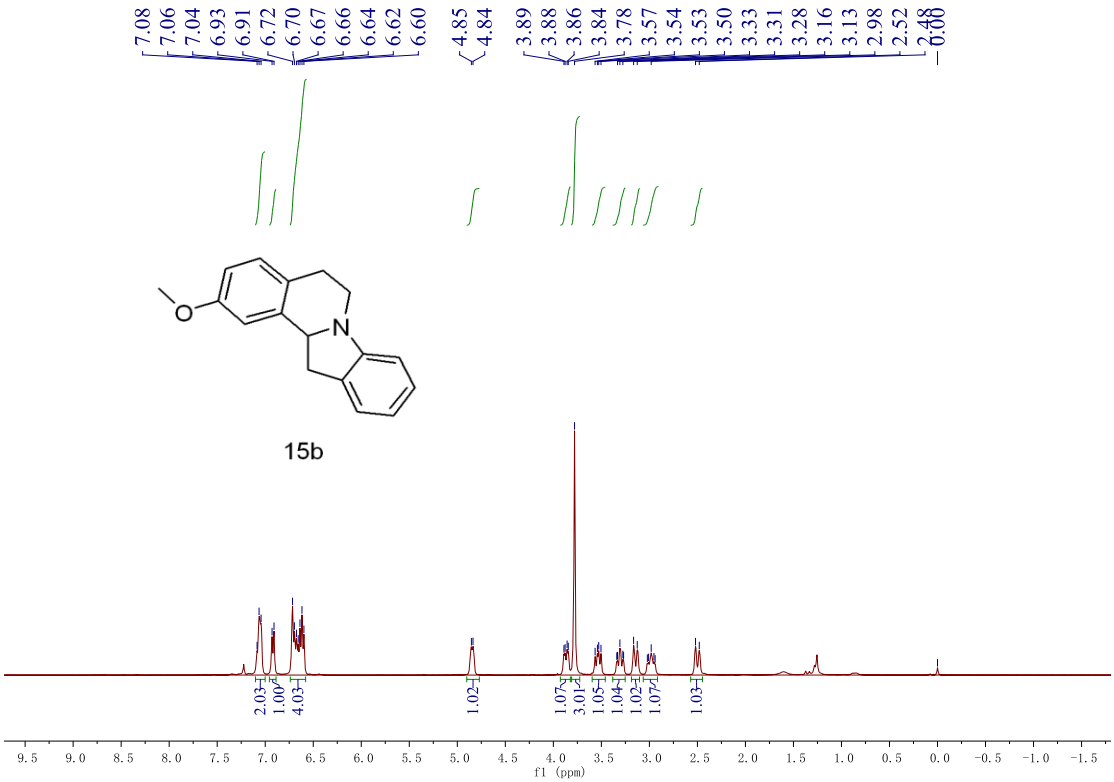

1.08
1.81
1.00
2.01
1.00
1.01
1.13
3.00
1.08
1.06
2.17
1.07
f1 (ppm)


157.8
150.4
136.2
131.3
129.7
127.3
127.0
124.9
118.0
113.3
112.8
107.4
62.4
55.2
42.1
36.9
25.7

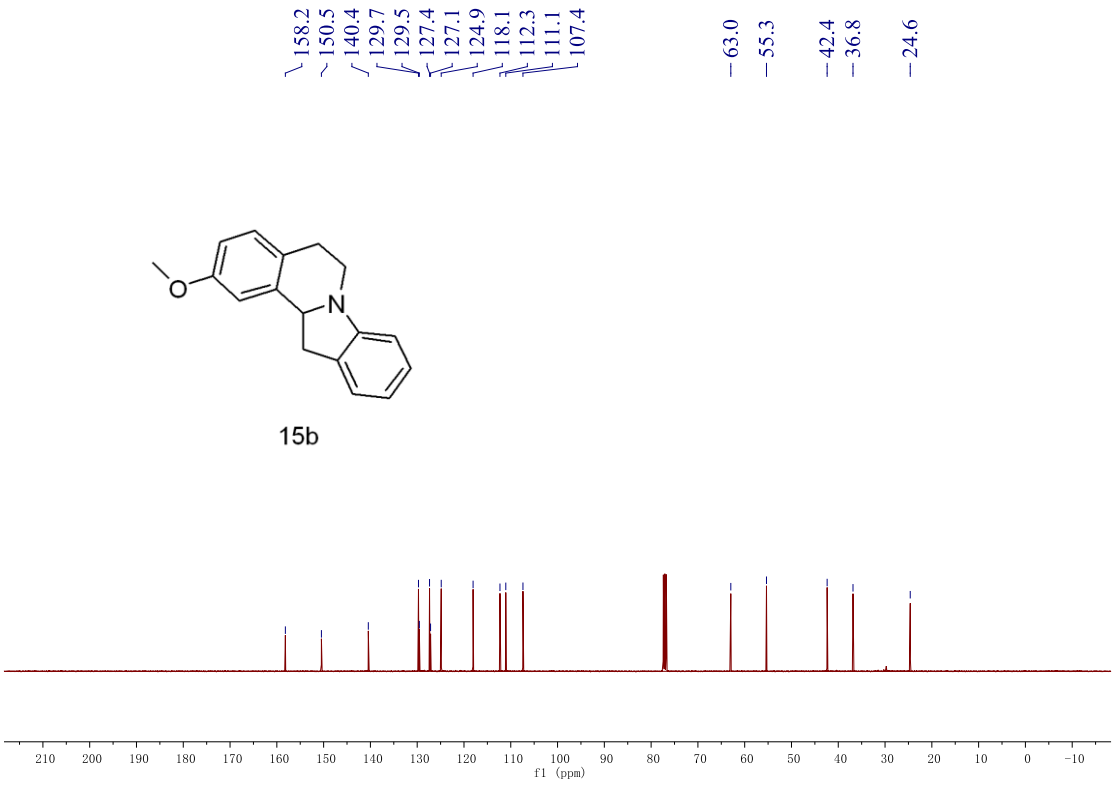

O
N

15a

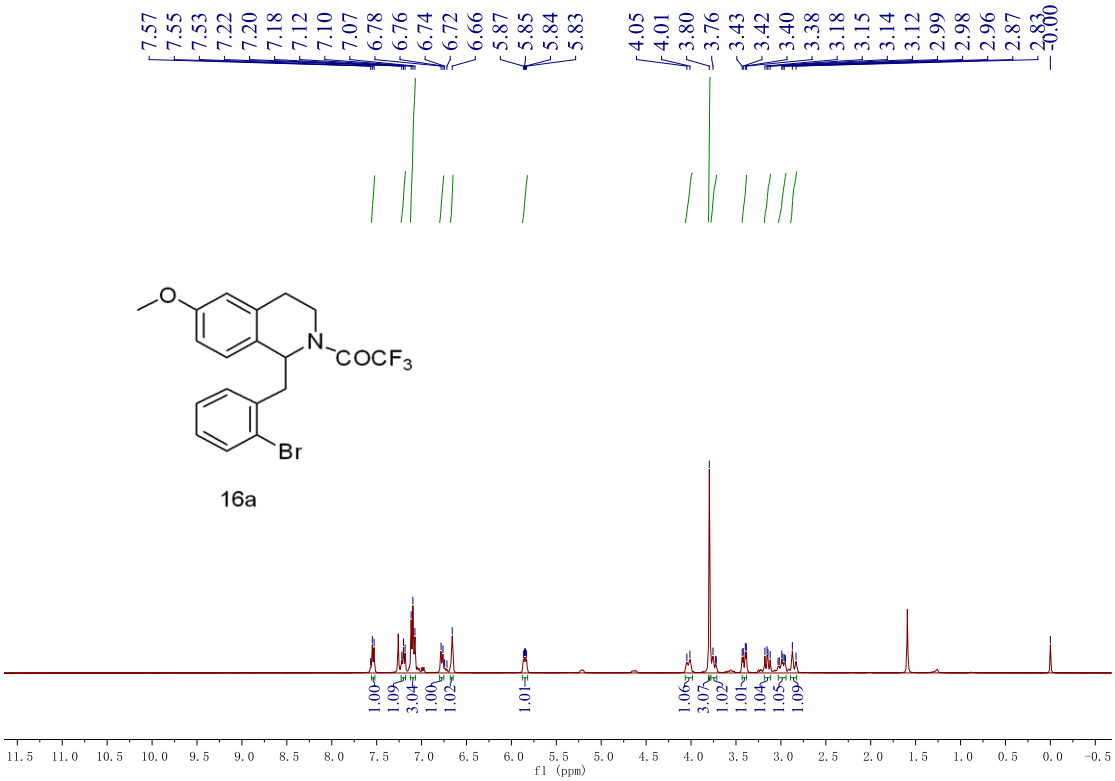

f1 (ppm)

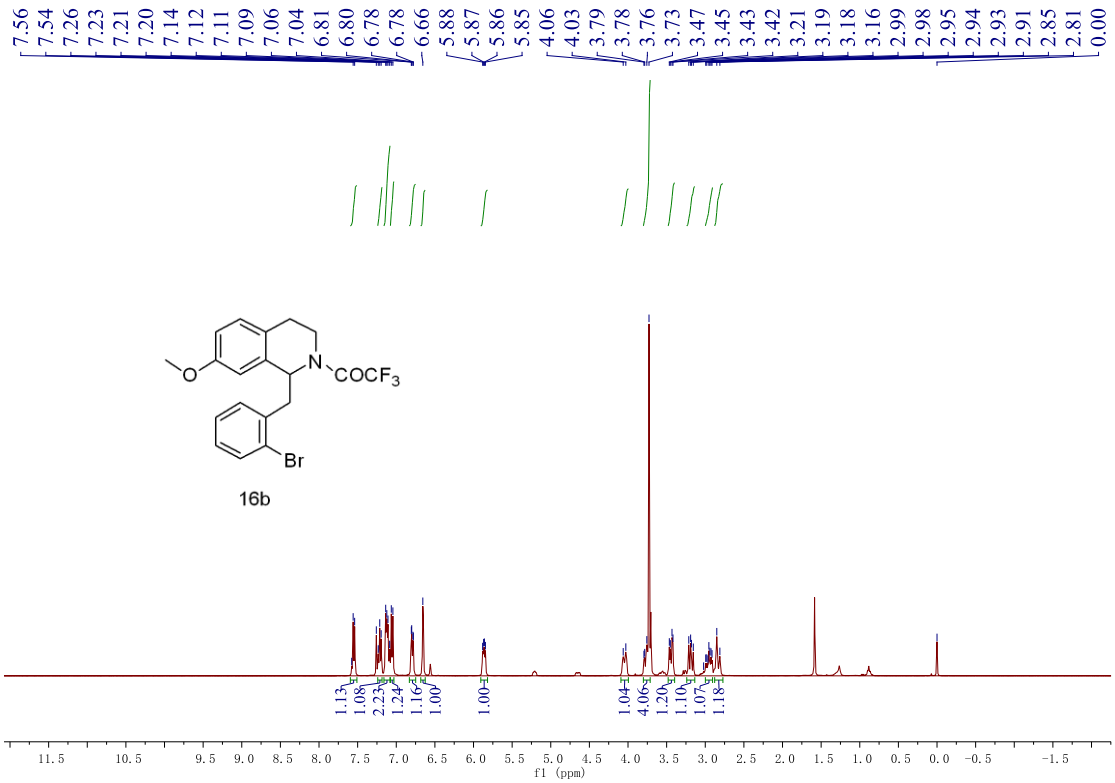

7.08
7.06
7.04
6.93
6.91
6.72
6.70
6.67
6.66
6.64
6.62
6.60
4.85
4.84
3.89
3.88
3.86
3.84
3.78
3.57
3.54
3.53
3.50
3.33
3.31
3.28
3.16
3.13
2.98
2.52
2.48
0.00
O
N
2.03
1.00
4.03
1.02
1.07
3.01
1.05
1.04
1.02
1.07
1.03
f1 (ppm)

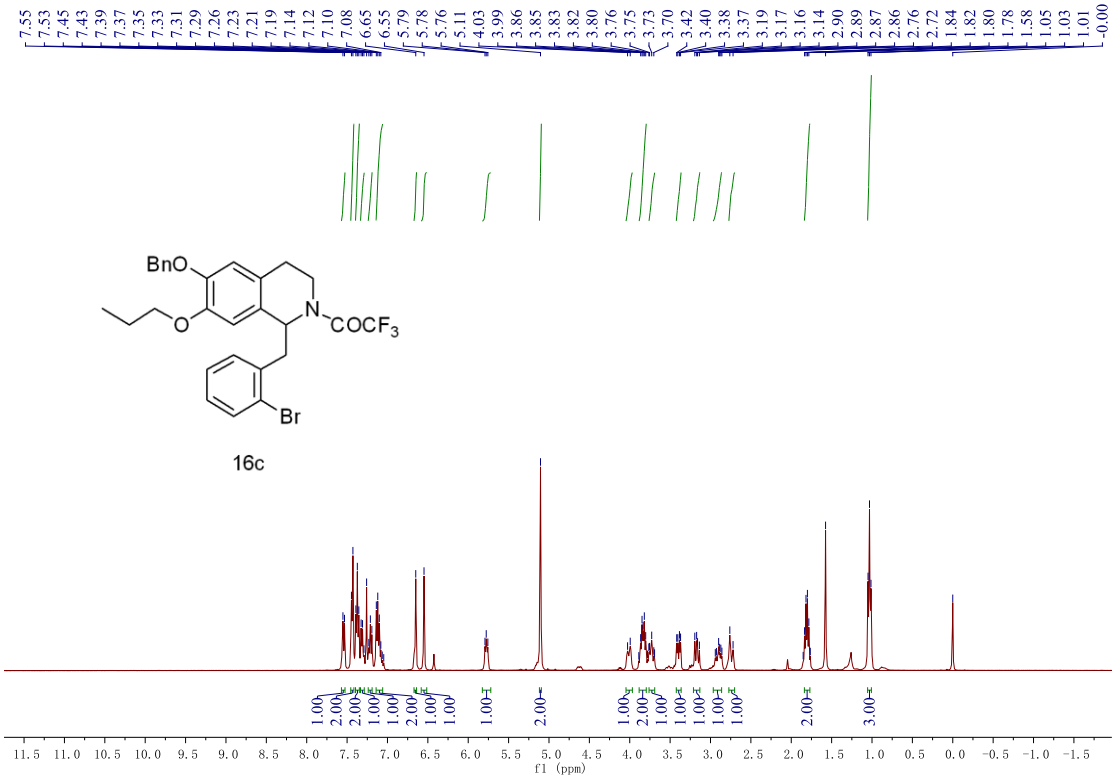
15b


158.2
150.5
140.4
129.7
129.5
127.4
127.1
124.9
118.1
112.3
111.1
107.4
63.0
55.3
42.4
36.8
24.6
O
N
f1 (ppm)

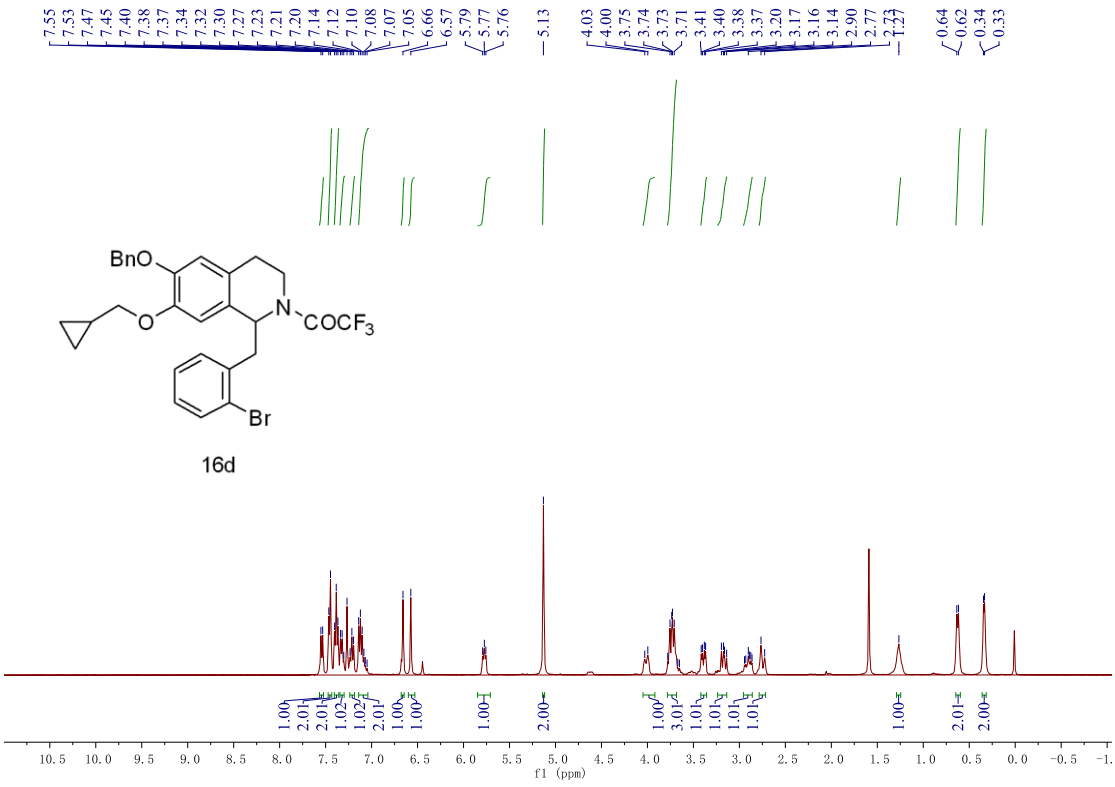
15b


7.57
7.55
7.53
7.22
7.20
7.18
7.12
7.10
7.07
6.78
6.76
6.74
6.72
6.66
5.87
5.85
5.84
5.83
4.05
4.01
3.80
3.76
3.43
3.42
3.40
3.38
3.18
3.15
3.14
3.12
2.99
2.98
2.96
2.87
2.83
0.00
O
N
COCF3
Br
16a
1.00
1.09
3.04
1.00
1.02
1.01
1.06
3.07
1.02
1.01
1.04
1.05
1.09
f1 (ppm)

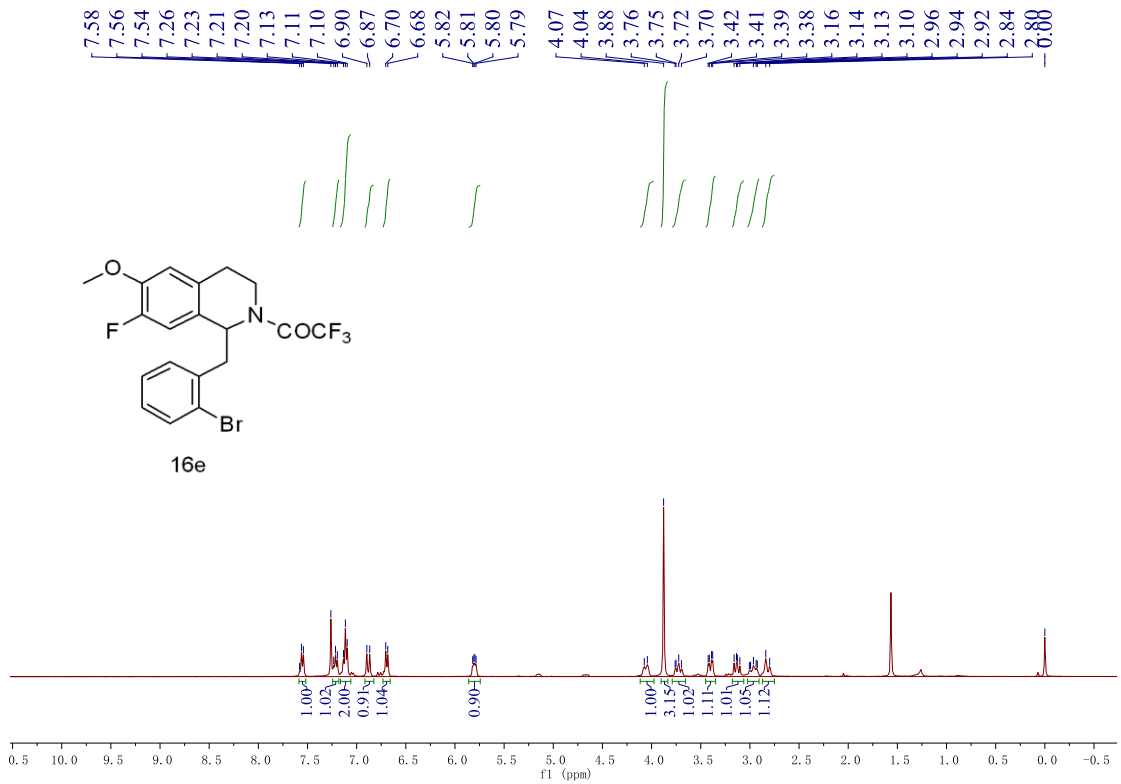

7.56
7.54
7.26
7.23
7.21
7.20
7.14
7.12
7.11
7.09
7.06
7.04
6.81
6.80
6.78
6.78
6.66
5.88
5.87
5.86
5.85
4.06
4.03
3.79
3.78
3.76
3.73
3.47
3.45
3.43
3.42
3.21
3.19
3.18
3.16
2.99
2.98
2.95
2.94
2.93
2.91
2.85
2.81
0.00
O
N
COCF3
Br
16b
1.13
1.08
2.23
1.24
1.16
1.00
1.00
1.04
4.06
1.20
1.10
1.07
1.18
f1 (ppm)



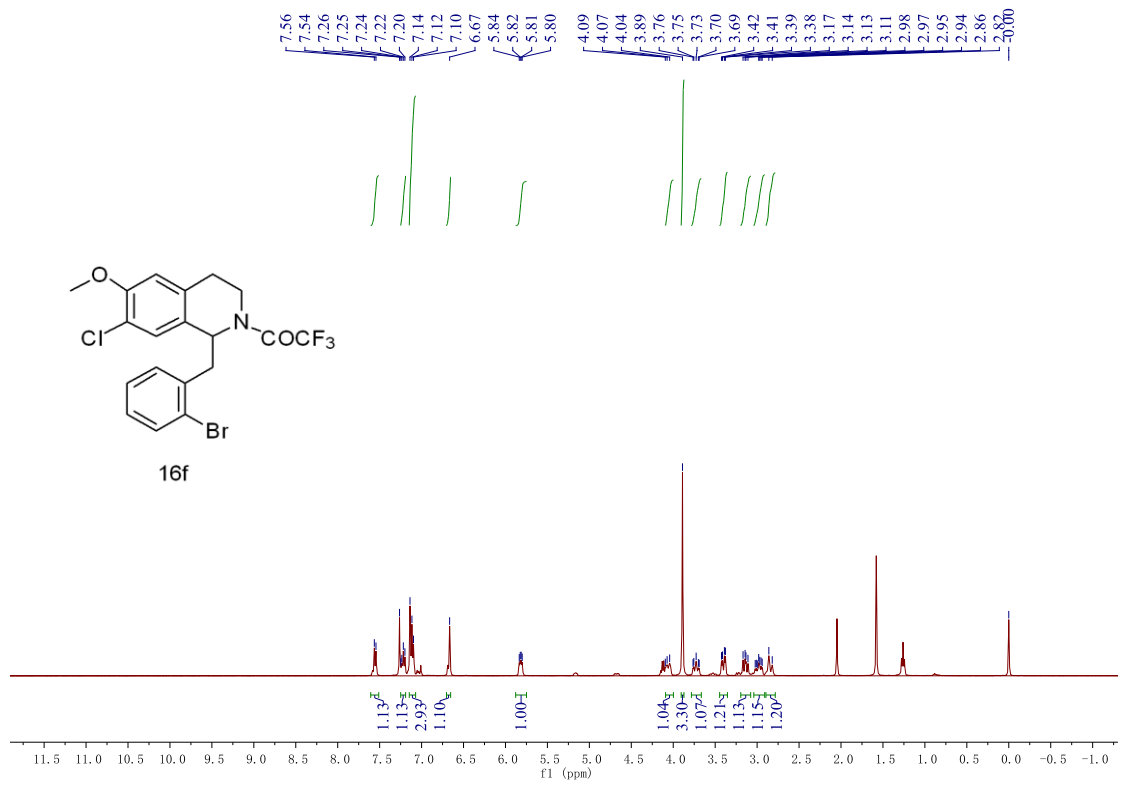
16c



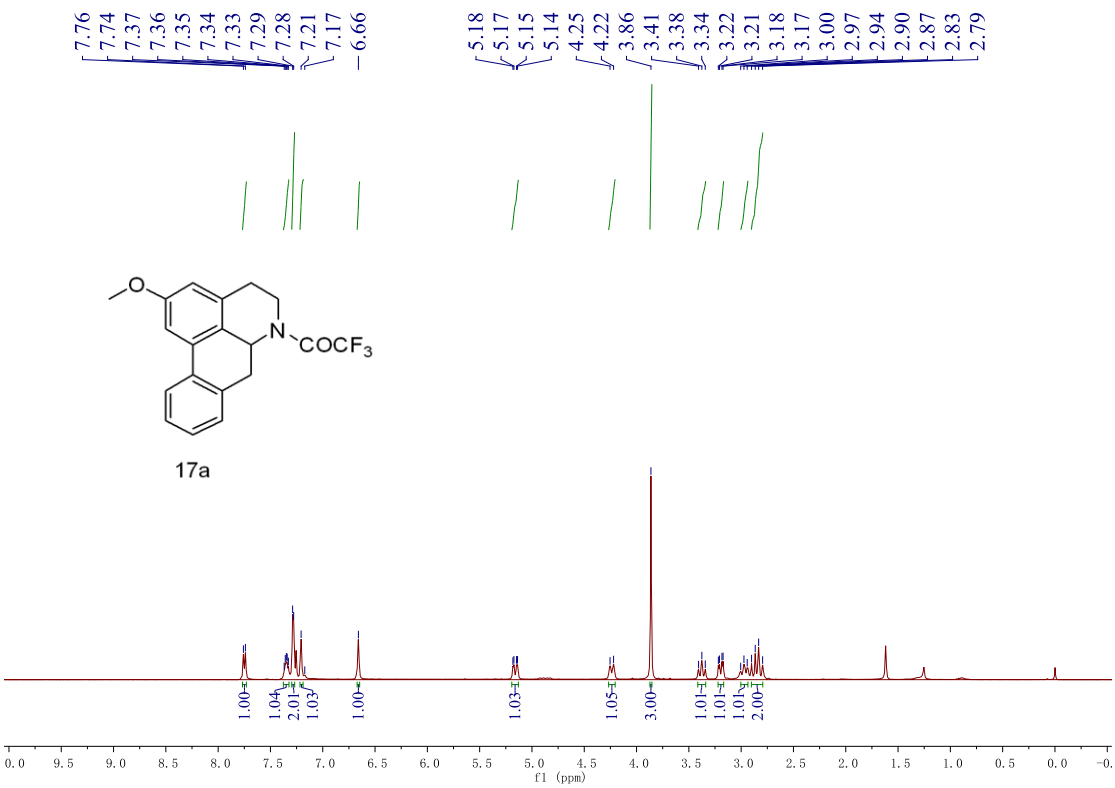
16d


7.58
7.56
7.54
7.26
7.23
7.21
7.20
7.13
7.11
7.10
6.90
6.87
6.70
6.68
5.82
5.81
5.80
5.79
4.07
4.04
3.88
3.76
3.75
3.72
3.70
3.42
3.41
3.39
3.38
3.16
3.14
3.13
3.10
2.96
2.94
2.92
2.84
2.80
0.00
O
F
N
COCF3
Br
1.00
1.02
2.00
0.91
1.04
0.90
1.00
3.15
1.02
1.11
1.01
1.05
1.12
f1 (ppm)

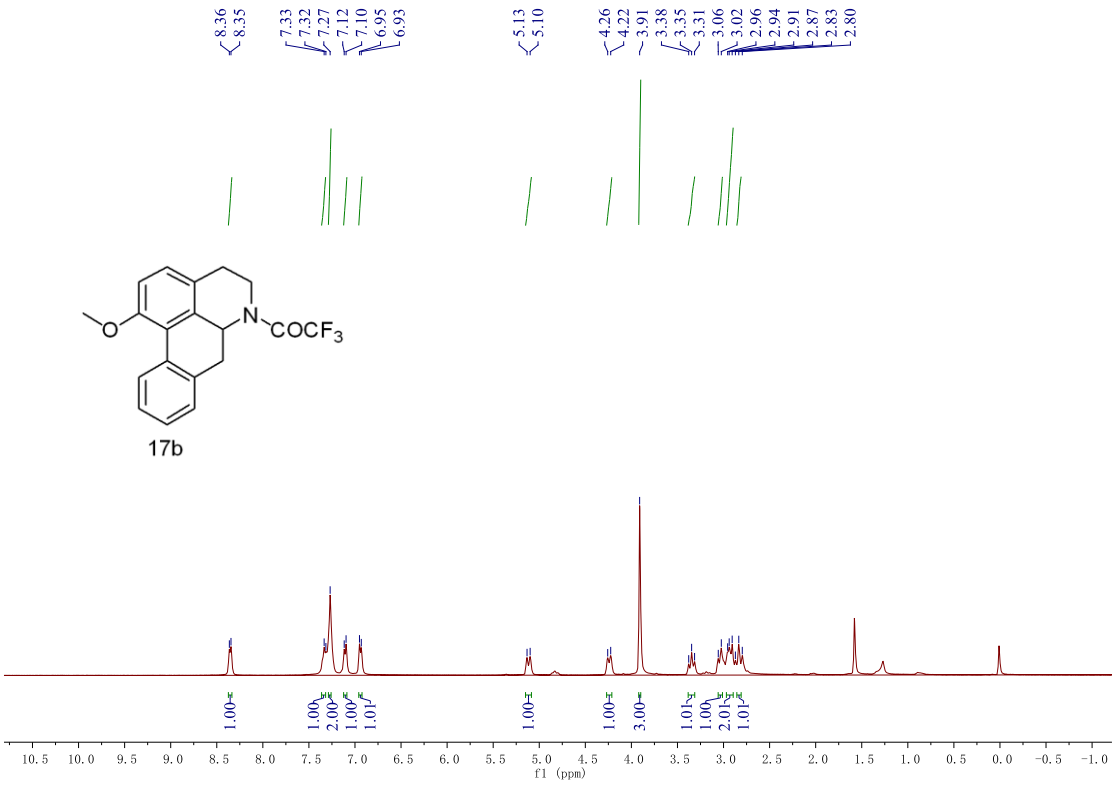
16e


7.56
7.54
7.26
7.25
7.24
7.22
7.20
7.14
7.12
7.10
6.67
5.84
5.82
5.81
5.80
4.09
4.07
4.04
3.89
3.76
3.75
3.73
3.70
3.69
3.42
3.41
3.39
3.38
3.17
3.14
3.13
3.11
2.98
2.97
2.95
2.94
2.86
2.82
20.00
O
Cl
N
COCF3
Br
1.13
1.13
2.93
1.10
1.00
1.04
3.30
1.07
1.21
1.13
1.15
1.20
f1 (ppm)

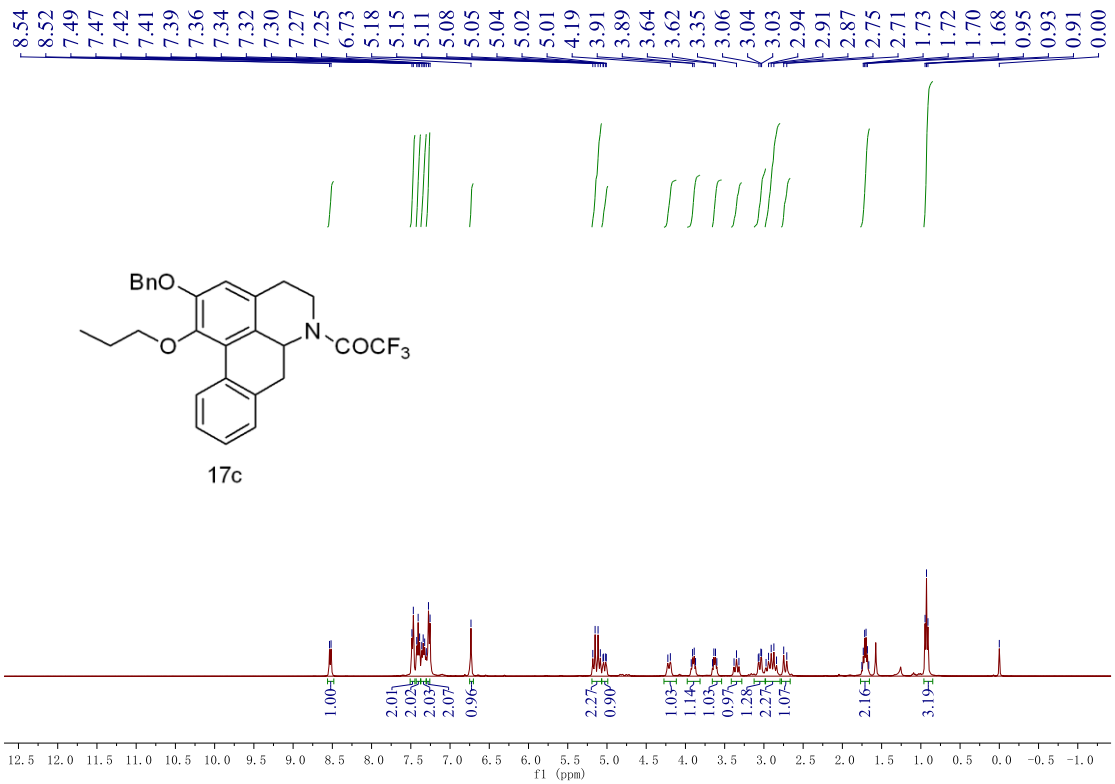
16f


7.76
7.74
7.37
7.36
7.35
7.34
7.33
7.29
7.28
7.21
7.17
6.66
5.18
5.17
5.15
5.14
4.25
4.22
3.86
3.41
3.38
3.34
3.22
3.21
3.18
3.17
3.00
2.97
2.94
2.90
2.87
2.83
2.79
O
N
COCF3
1.00
1.04
2.01
1.03
1.00
1.03
1.05
3.00
1.01
1.01
1.01
2.00
f1 (ppm)

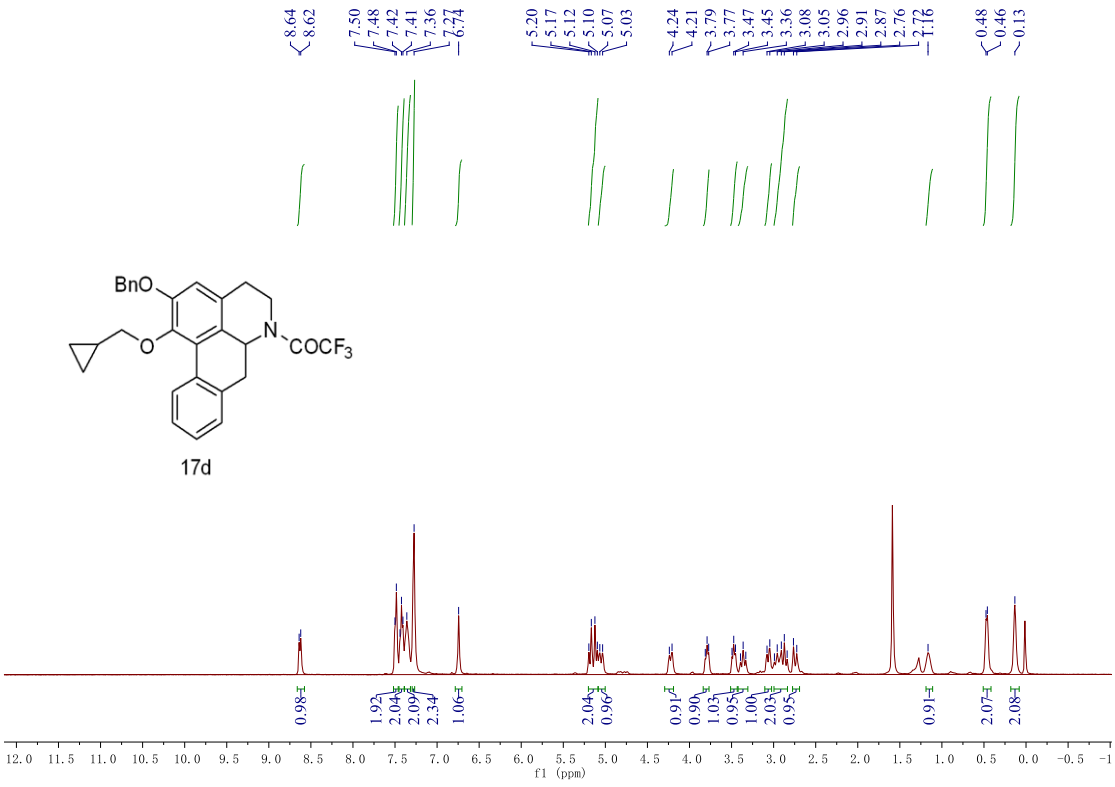
17a


8.36
8.35
7.33
7.32
7.27
7.12
7.10
6.95
6.93
5.13
5.10
4.26
4.22
3.91
3.38
3.35
3.31
3.06
3.02
2.96
2.94
2.91
2.87
2.83
2.80
O
N
COCF3
1.00
1.00
2.00
1.00
1.01
1.00
1.00
3.00
1.01
1.00
2.01
1.01
f1 (ppm)

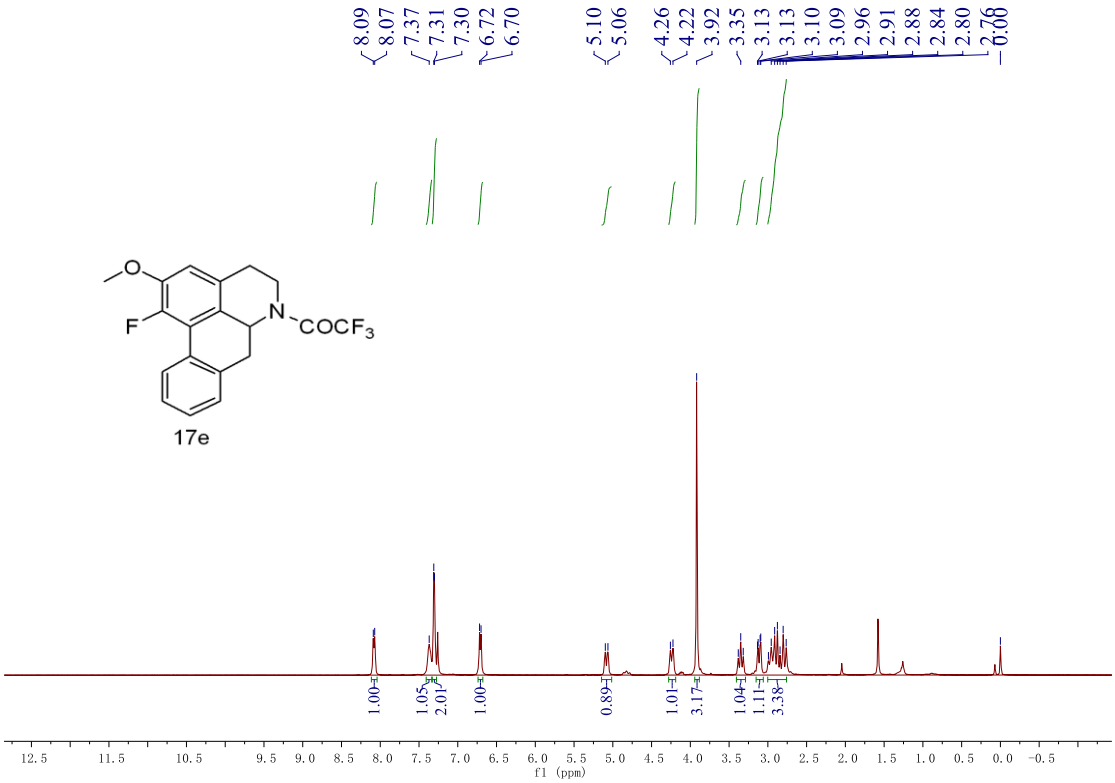
17b

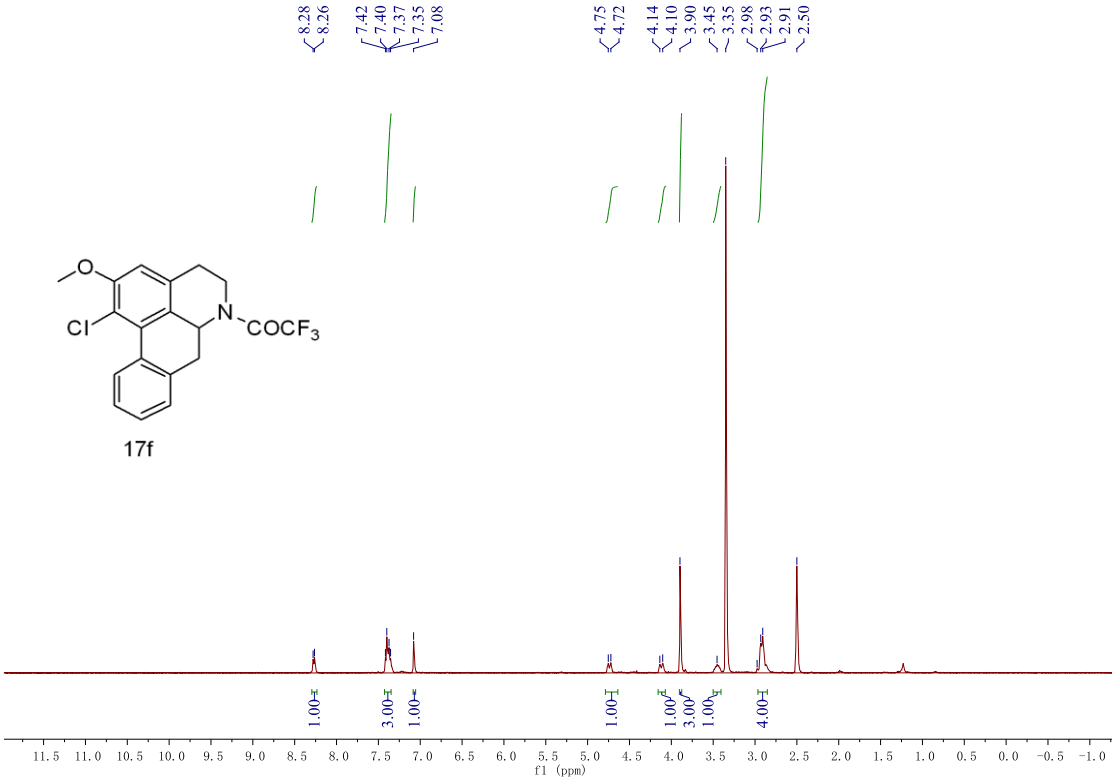

8.54
8.52
7.49
7.47
7.42
7.41
7.39
7.36
7.34
7.32
7.30
7.27
7.25
6.73
5.18
5.15
5.11
5.08
5.05
5.04
5.02
5.01
4.19
3.91
3.89
3.64
3.62
3.35
3.06
3.04
3.03
2.94
2.91
2.87
2.75
2.71
1.73
1.72
1.70
1.68
0.95
0.93
0.91
0.00
BnO
O
N
COCF3
1.00
2.01
2.02
2.03
2.07
0.96
2.27
0.90
1.03
1.14
1.03
0.97
1.28
2.27
1.07
2.16
3.19
f1 (ppm)

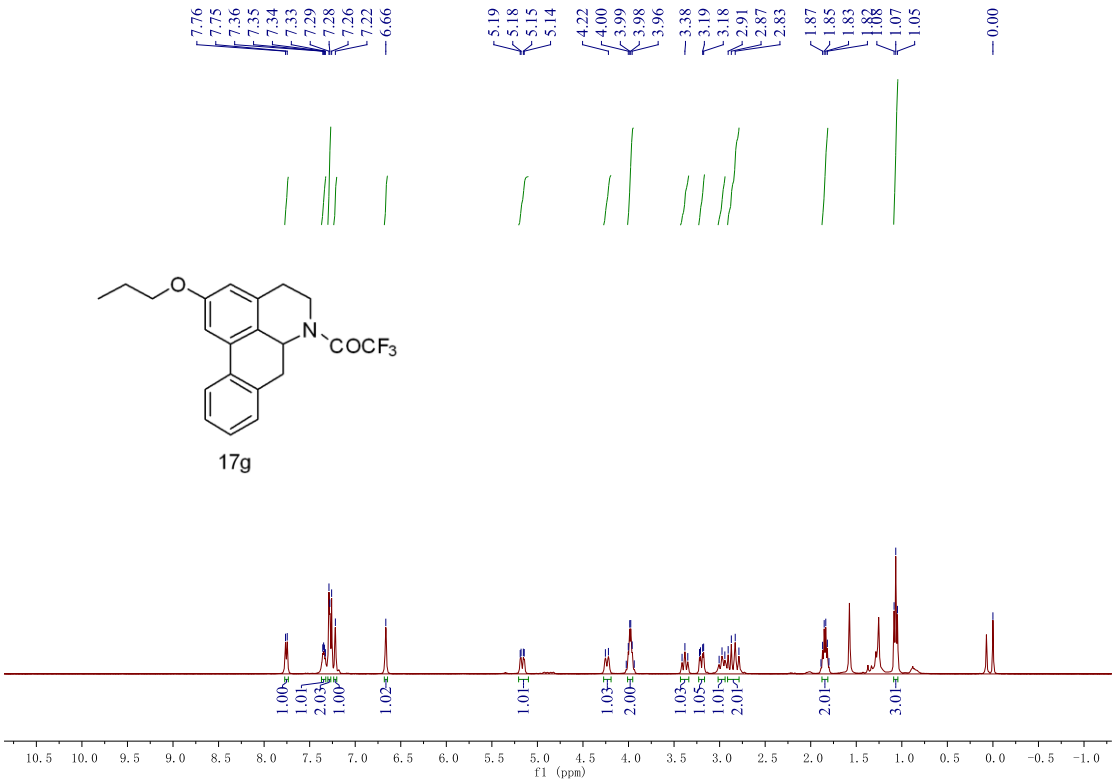
17c

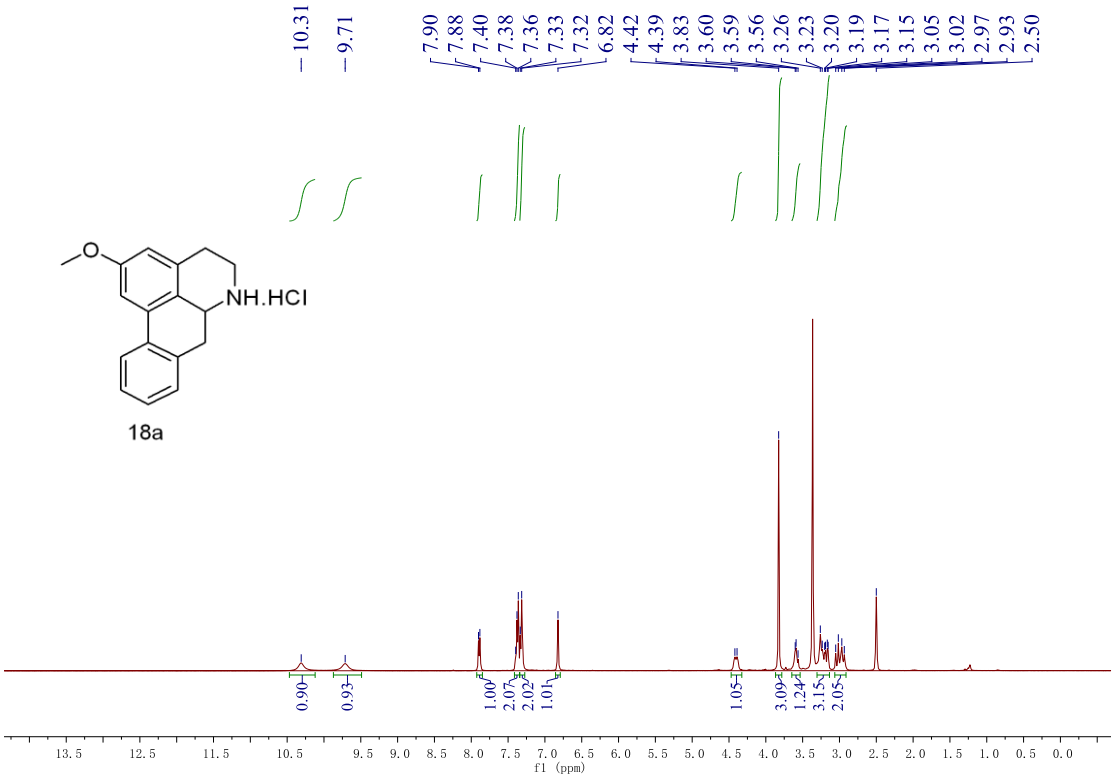

8.64
8.62
7.50
7.48
7.42
7.41
7.36
7.27
6.74
5.20
5.17
5.12
5.10
5.07
5.03
4.24
4.21
3.79
3.77
3.47
3.45
3.36
3.08
3.05
2.96
2.91
2.87
2.76
2.72
1.16
0.48
0.46
0.13
BnO
O
N
COCF3
0.98
1.92
2.04
2.09
2.34
1.06
2.04
0.96
0.91
0.90
1.03
0.95
1.00
2.03
0.95
0.91
2.07
2.08
f1 (ppm)

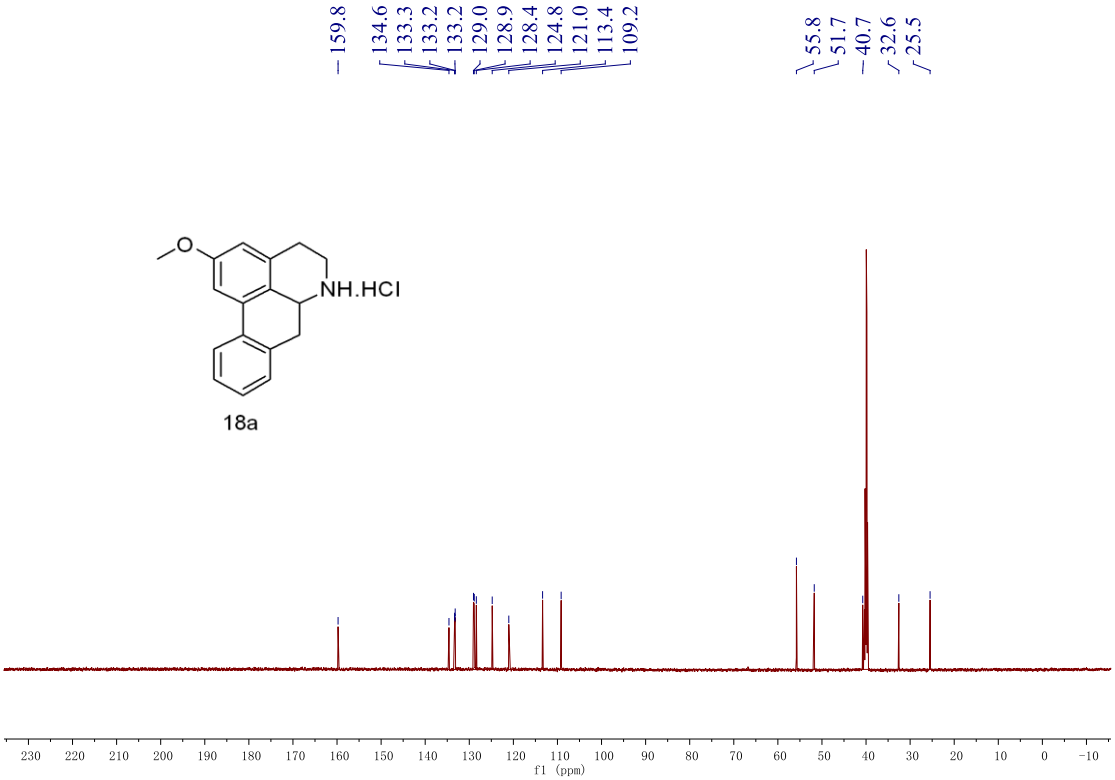
17d

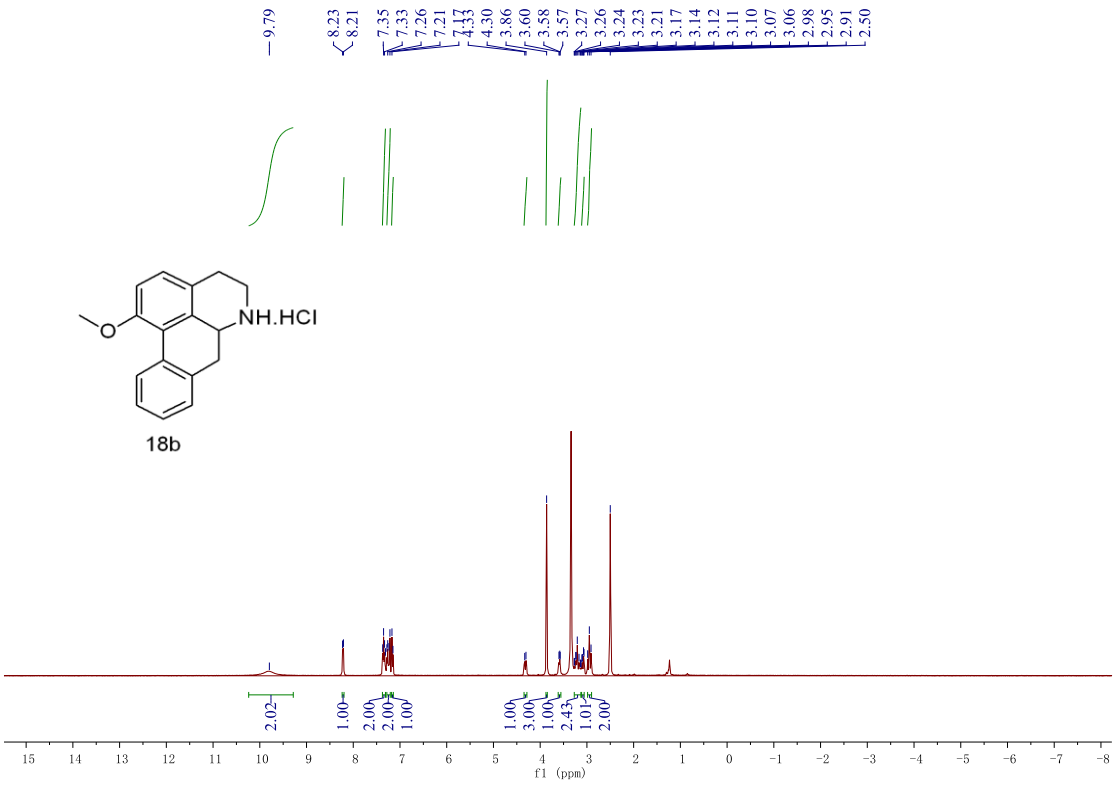

8.09
8.07
7.37
7.31
7.30
6.72
6.70
5.10
5.06
4.26
4.22
3.92
3.35
3.13
3.13
3.10
3.09
2.96
2.91
2.88
2.84
2.80
2.76
0.00
O
F
N
COCF3
17e
1.00
1.05
2.01
1.00
0.89
1.01
3.17
1.04
1.11
3.38
f1 (ppm)

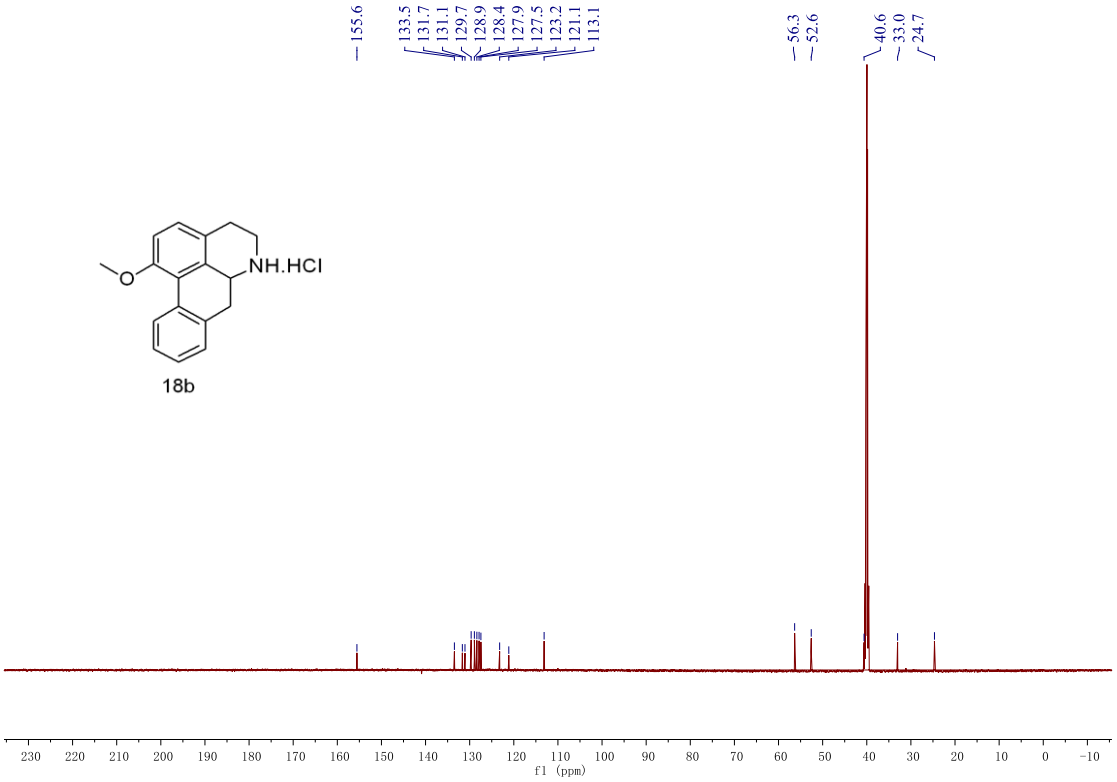

8.28
8.26
7.42
7.40
7.37
7.35
7.08
4.75
4.72
4.14
4.10
3.90
3.45
3.35
2.98
2.93
2.91
2.50
O
Cl
N
COCF3
17f
1.00
3.00
1.00
1.00
1.00
3.00
1.00
4.00
f1 (ppm)

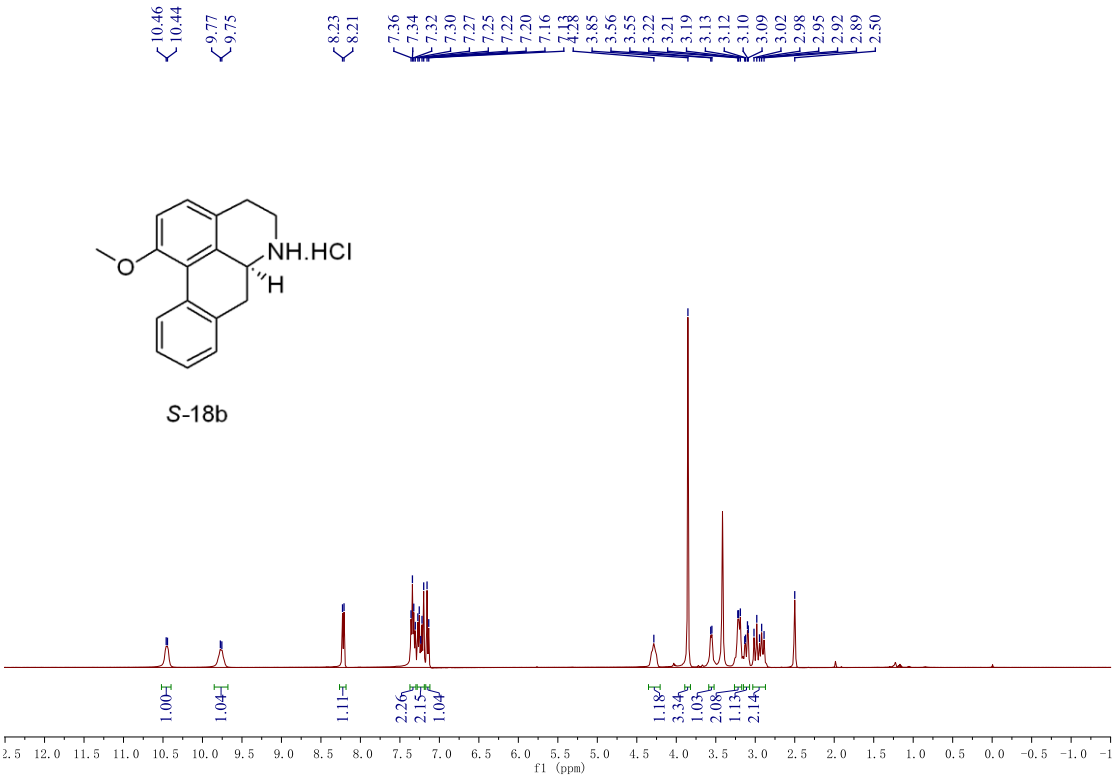

7.76
7.75
7.36
7.35
7.34
7.33
7.29
7.28
7.26
7.22
6.66
5.19
5.18
5.15
5.14
4.22
4.00
3.99
3.98
3.96
3.38
3.19
3.18
2.91
2.87
2.83
1.87
1.85
1.83
1.07
1.05
0.00
O
N
COCF3
17g
1.00
1.01
2.03
1.00
1.02
1.01
1.03
2.00
1.03
1.05
1.01
2.01
2.01
3.01
f1 (ppm)

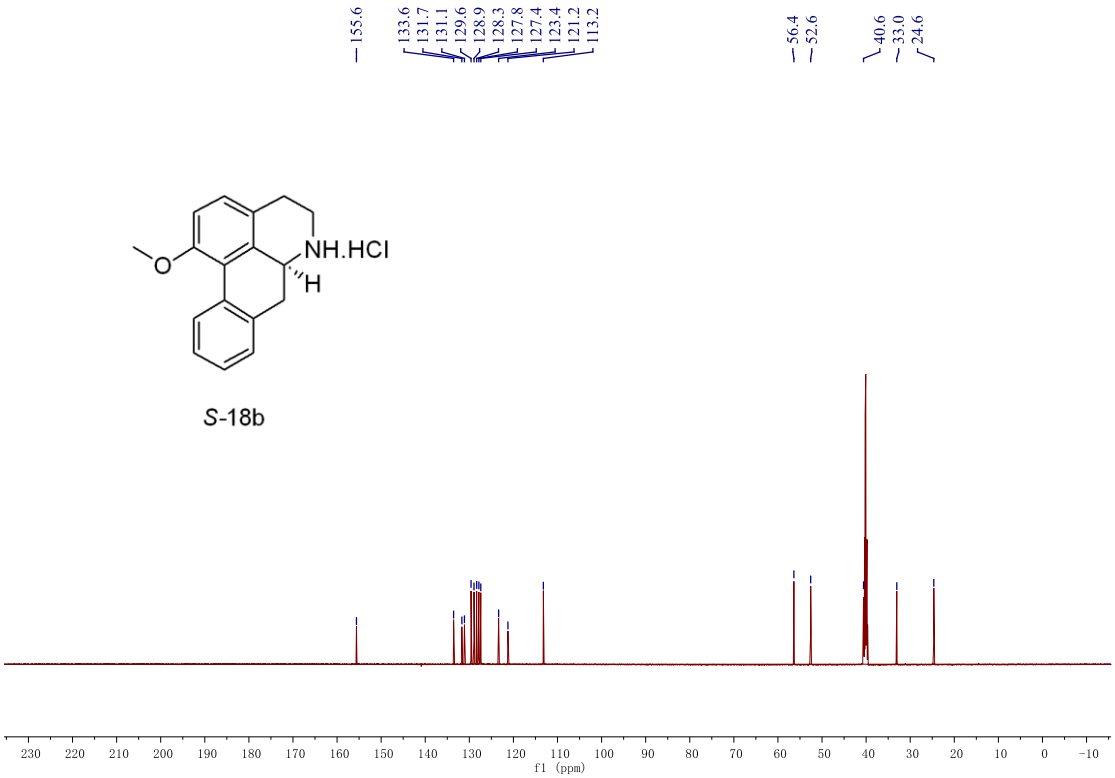

10.31
9.71
7.90
7.88
7.40
7.38
7.36
7.33
7.32
6.82
4.42
4.39
3.83
3.60
3.59
3.56
3.26
3.23
3.20
3.19
3.17
3.15
3.05
3.02
2.97
2.93
2.50
O
NH.HCl
18a
0.90
0.93
1.00
2.07
2.02
1.01
1.05
3.09
1.24
3.15
2.05
f1 (ppm)


159.8
134.6
133.3
133.2
133.2
129.0
128.9
128.4
124.8
121.0
113.4
109.2
55.8
51.7
40.7
32.6
25.5
O
NH.HCl
18a
f1 (ppm)

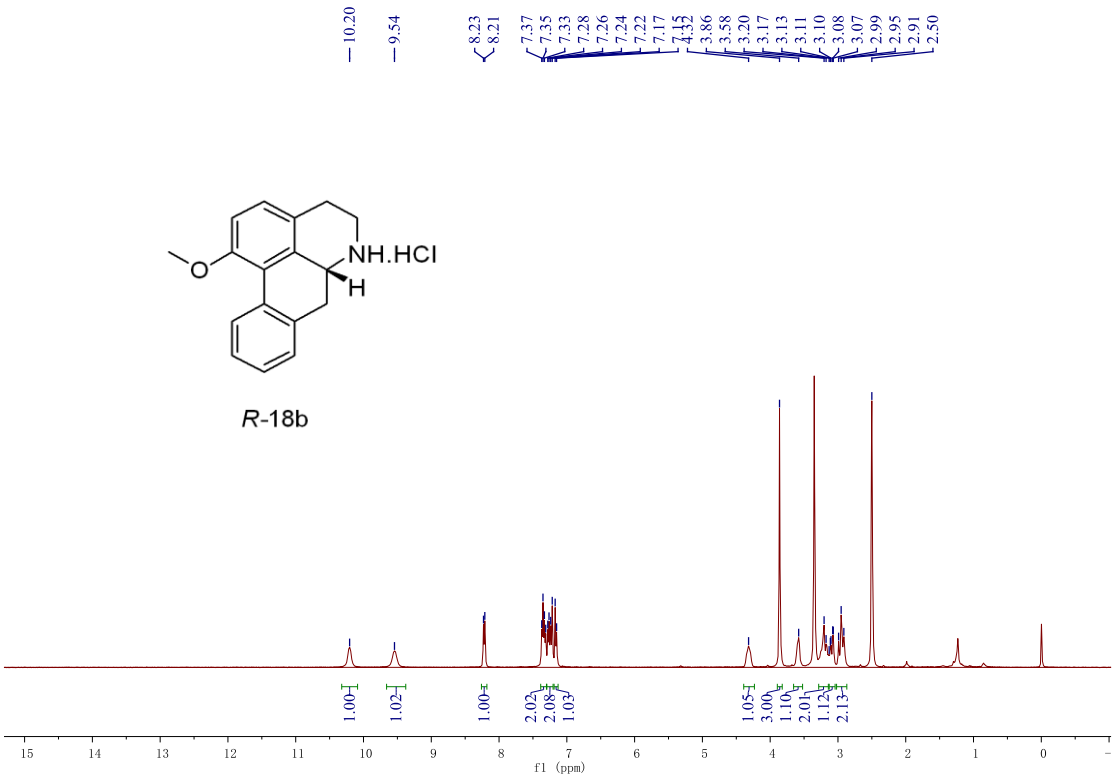

9.79
8.23
8.21
7.35
7.33
7.26
7.21
7.17
4.33
4.30
3.86
3.60
3.58
3.57
3.27
3.26
3.24
3.23
3.21
3.17
3.14
3.12
3.11
3.10
3.07
3.06
2.98
2.95
2.91
2.50
O
NH.HCl
18b
2.02
1.00
2.00
2.00
1.00
1.00
3.00
1.00
2.43
1.01
2.00
f1 (ppm)


155.6
133.5
131.7
131.1
129.7
128.9
128.4
127.9
127.5
123.2
121.1
113.1
56.3
52.6
40.6
33.0
24.7
NH.HCl
O
18b
f1 (ppm)

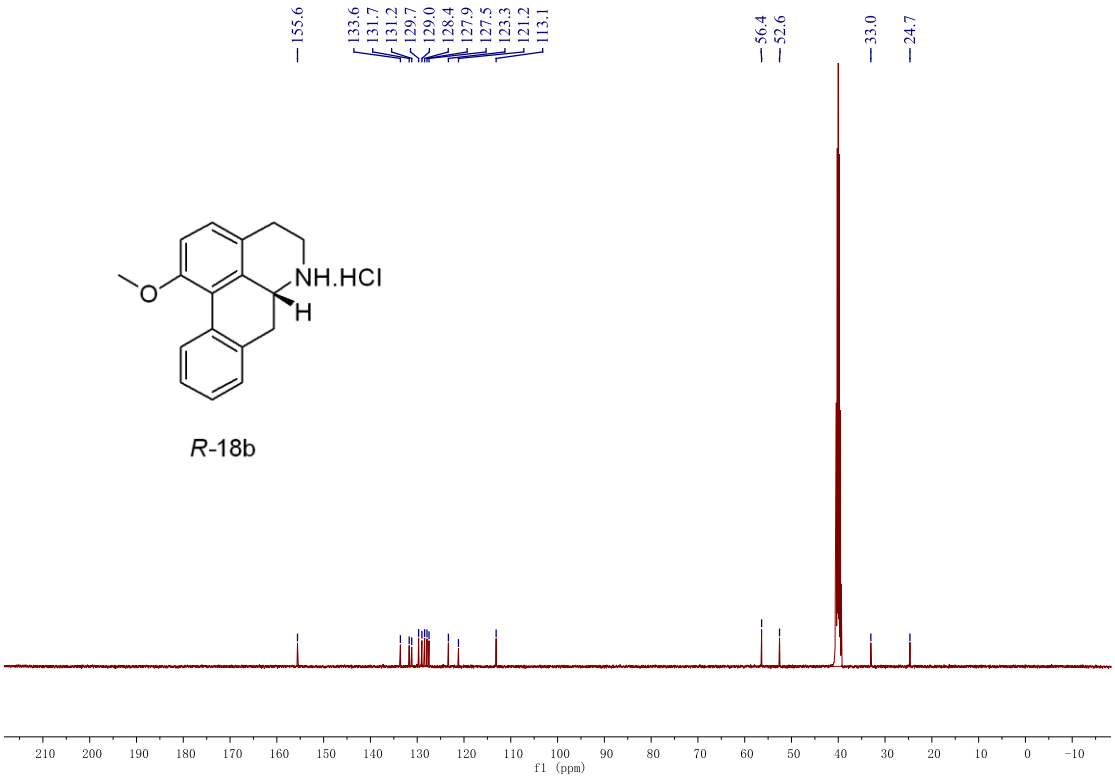

10.46
10.44
9.77
9.75
8.23
8.21
7.36
7.34
7.32
7.30
7.27
7.25
7.22
7.20
7.16
3.85
3.56
3.55
3.22
3.21
3.19
3.13
3.12
3.10
3.09
3.02
2.98
2.95
2.92
2.89
2.50
NH.HCl
H
O
S-18b
1.00
1.04
1.11
2.26
2.15
1.04
1.18
3.34
1.03
2.08
1.13
2.14
f1 (ppm)


155.6
133.6
131.7
131.1
129.6
128.9
128.3
127.8
127.4
123.4
121.2
113.2
56.4
52.6
40.6
33.0
24.6
NH.HCl
H
O
f1 (ppm)

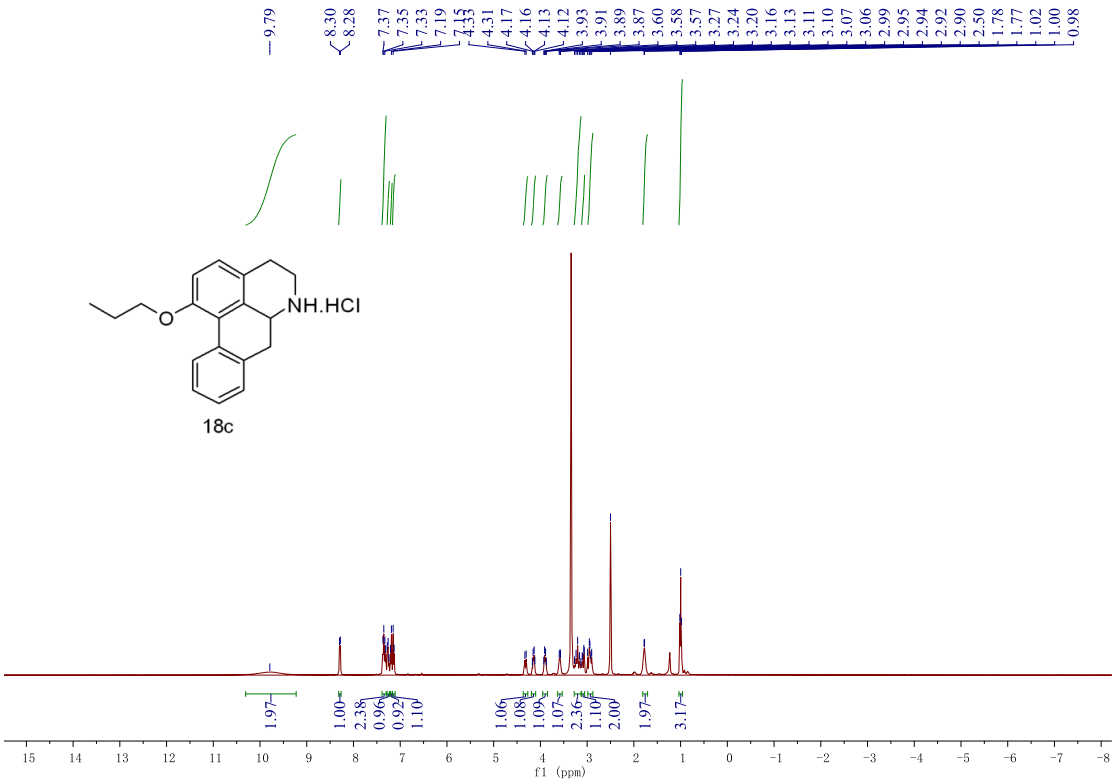
S-18b


10.20
9.54
8.23
8.21
7.37
7.35
7.33
7.28
7.26
7.24
7.22
7.17
4.32
3.86
3.58
3.20
3.17
3.13
3.11
3.10
3.08
3.07
2.99
2.95
2.91
2.50
NH.HCl
H
O
1.00
1.02
1.00
2.02
2.08
1.03
1.05
3.00
1.10
2.01
1.12
2.13
f1 (ppm)

R-18b


155.6
133.6
131.7
131.2
129.7
129.0
128.4
127.9
127.5
123.3
121.2
113.1
56.4
52.6
33.0
24.7
NH.HCl
H
O
f1 (ppm)

R-18b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4.31
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4.13
4.12
3.93
3.91
3.89
3.87
3.60
3.58
3.57
3.27
3.24
3.20
3.16
3.13
3.11
3.10
3.07
3.06
2.99
2.95
2.94
2.92
2.90
2.50
1.78
1.77
1.02
1.00
0.98
NH.HCl
O
1.97
1.00
2.38
0.96
0.92
1.10
1.06
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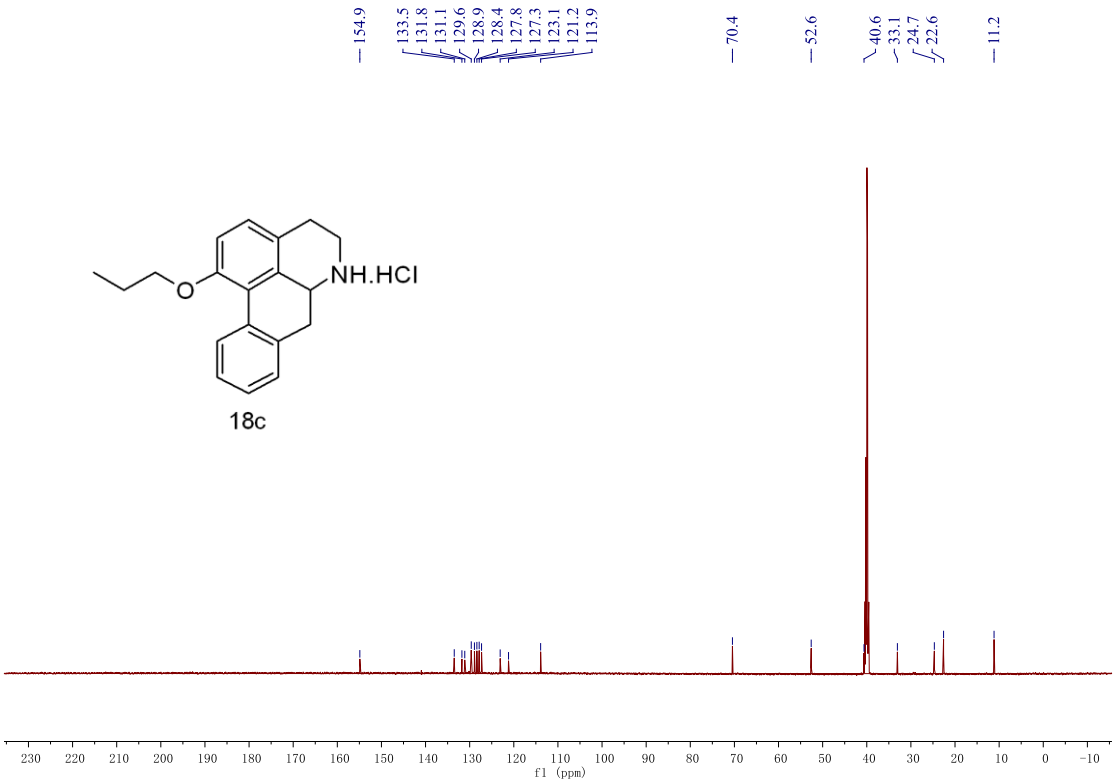
1.09
1.07
2.36
1.10
2.00
1.97
3.17
f1 (ppm)

18c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128.9
128.4
127.8
127.3
123.1
121.2
113.9
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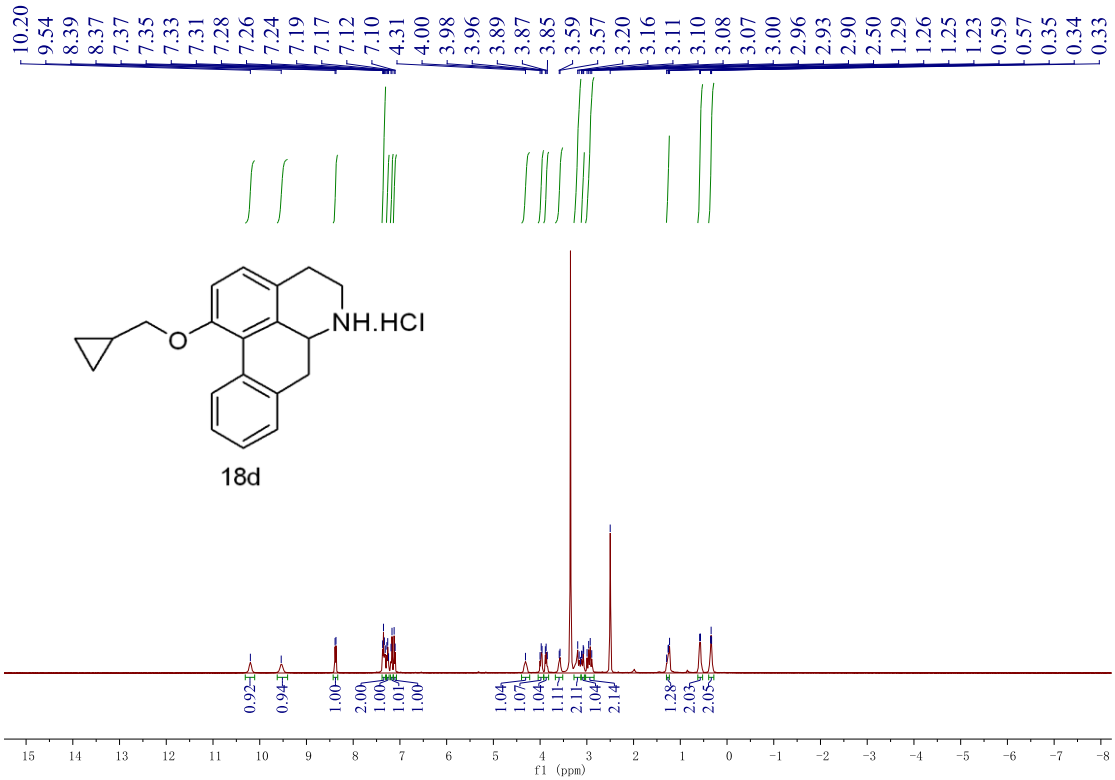
40.6
33.1
24.7
22.6
11.2
NH.HCl
O
18c
f1 (ppm)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7.26
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7.17
7.12
7.10
4.31
4.00
3.98
3.96
3.89
3.87
3.85
3.59
3.57
3.20
3.16
3.11
3.10
3.08
3.07
3.00
2.96
2.93
2.90
2.50
1.29
1.26
1.25
1.23
0.59
0.57
0.35
0.34
0.33
NH.HCl
O
18d
0.92
0.94
1.00
2.00
1.00
1.01
1.00
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1.07
1.04
1.11
2.11
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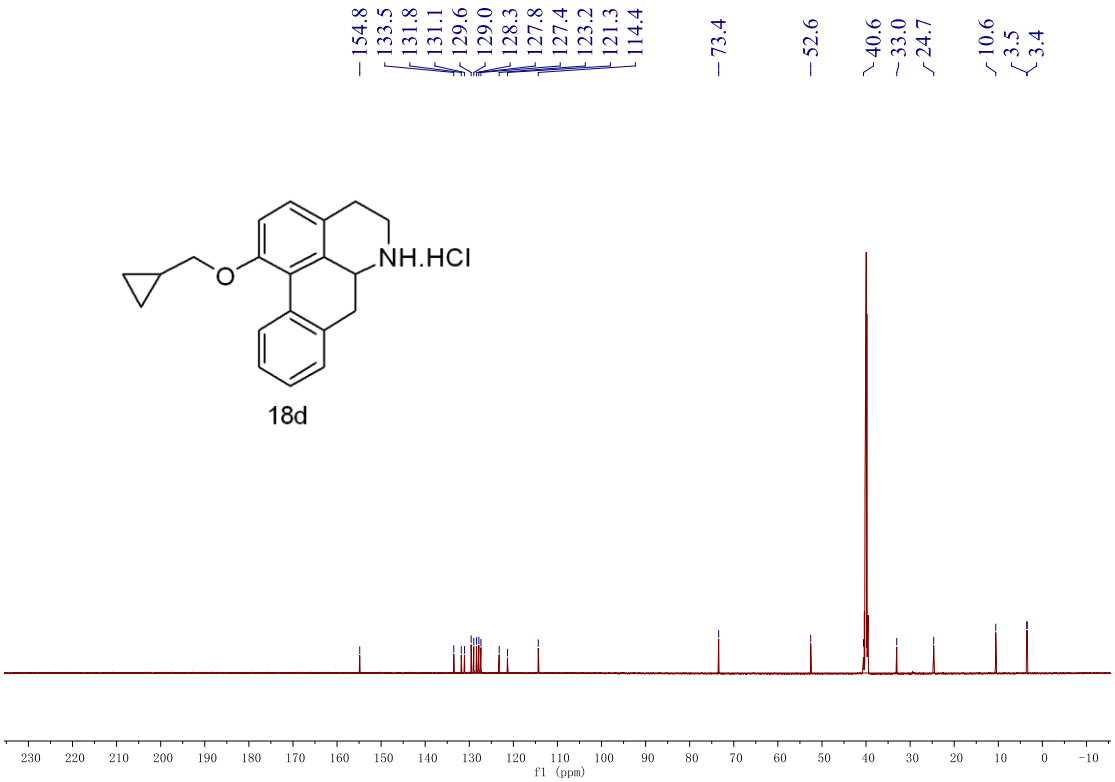
2.05
f1 (ppm)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128.3
127.8
127.4
123.2
121.3
114.4
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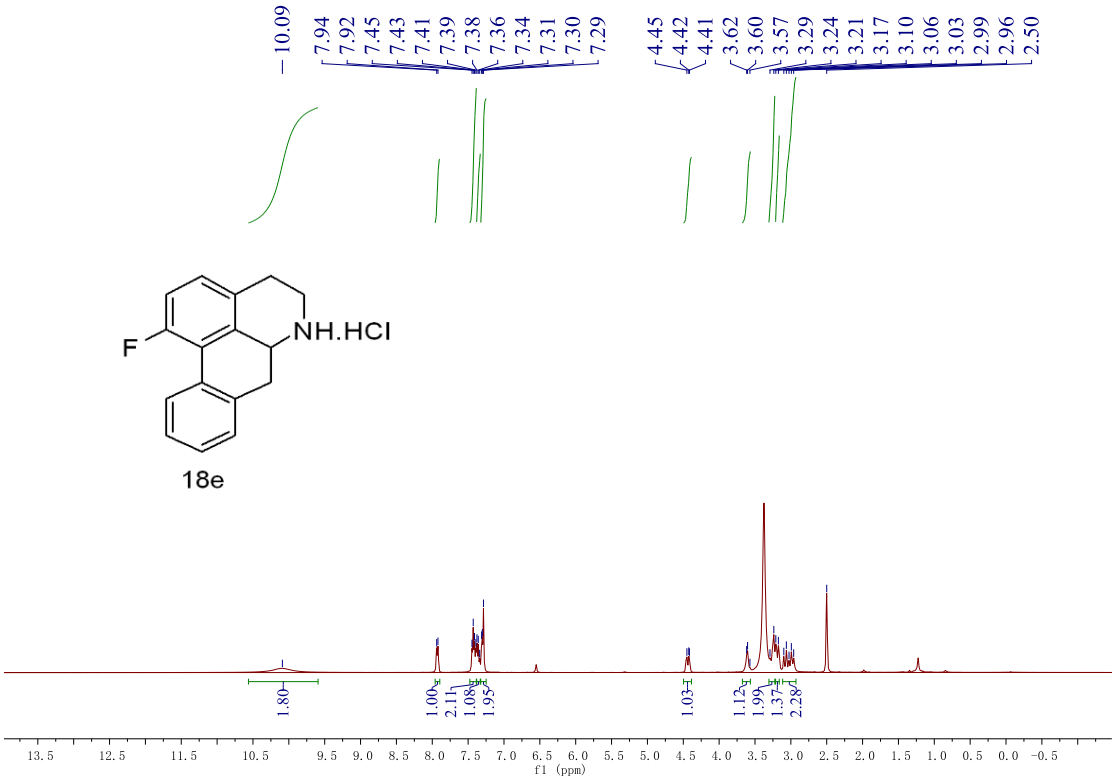
40.6
33.0
24.7
10.6
3.5
3.4
NH.HCl
O
18d
f1 (ppm)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7.38
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7.34
7.31
7.30
7.29
4.45
4.42
4.41
3.62
3.60
3.57
3.29
3.24
3.21
3.17
3.10
3.06
3.03
2.99
2.96
2.50
NH.HCl
F
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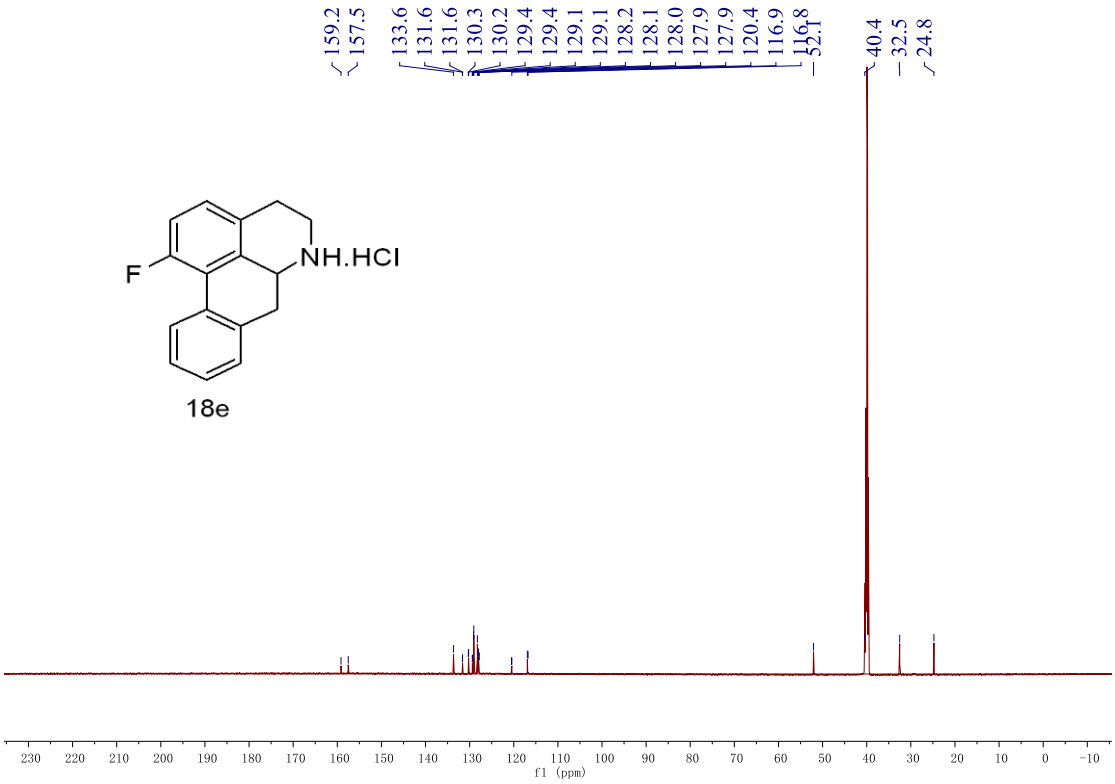
1.95
1.03
1.12
1.99
1.37
2.28
f1 (ppm)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129.1
129.1
128.2
128.1
128.0
127.9
127.9
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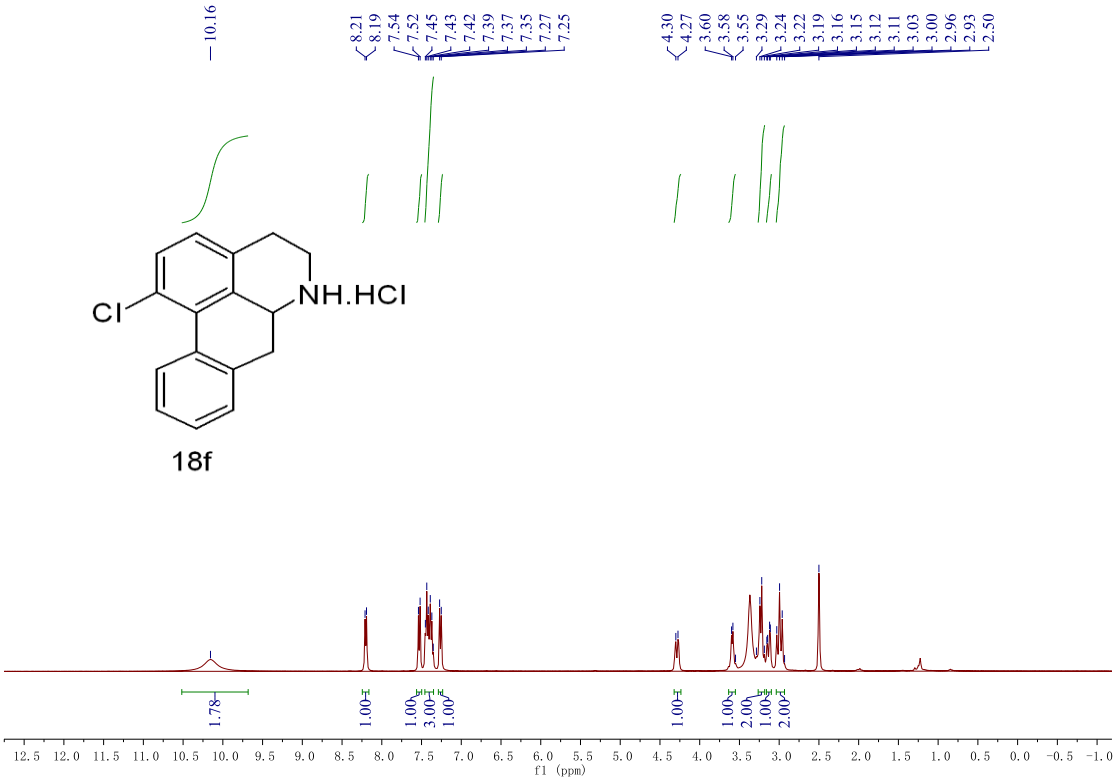
116.9
116.8
52.1
40.4
32.5
24.8
F
NH.HCl
18e
f1 (ppm)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7.25
4.30
4.27
3.60
3.58
3.55
3.29
3.24
3.22
3.19
3.16
3.15
3.12
3.11
3.03
3.00
2.96
2.93
2.50
Cl
NH.HCl
18f
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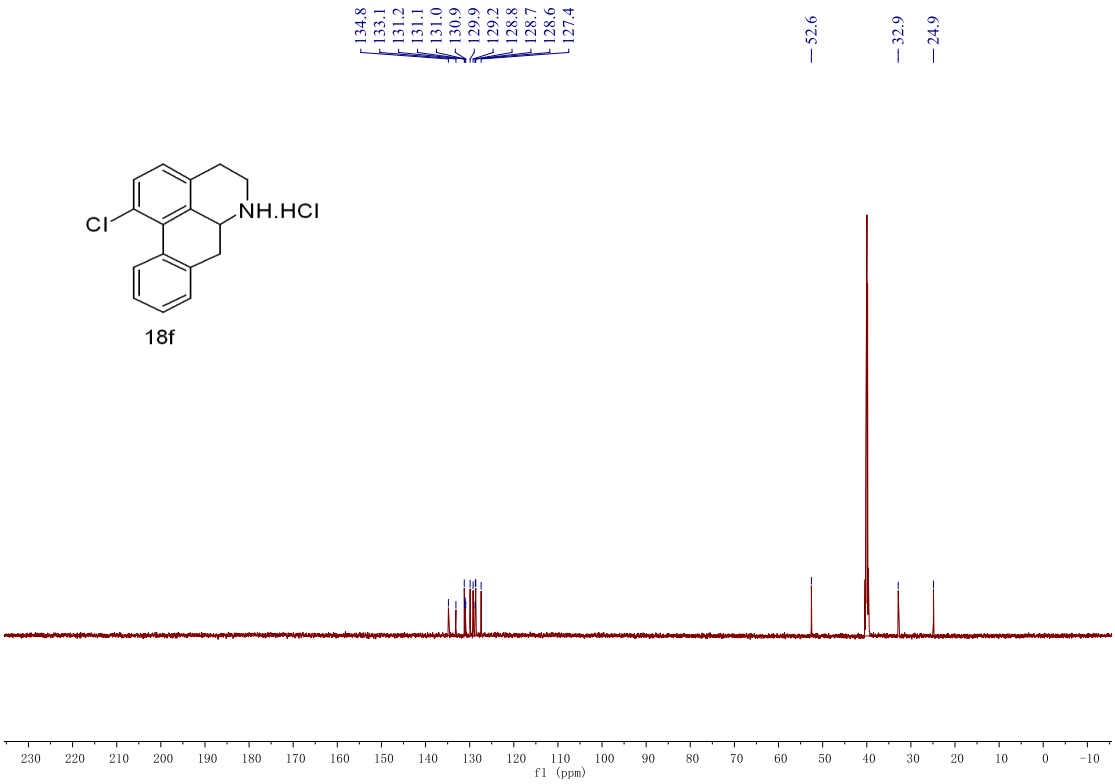
1.00
1.00
3.00
1.00
1.00
2.00
1.00
2.00
f1 (ppm)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131.2
131.1
131.0
130.9
129.9
129.2
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128.7
128.6
127.4
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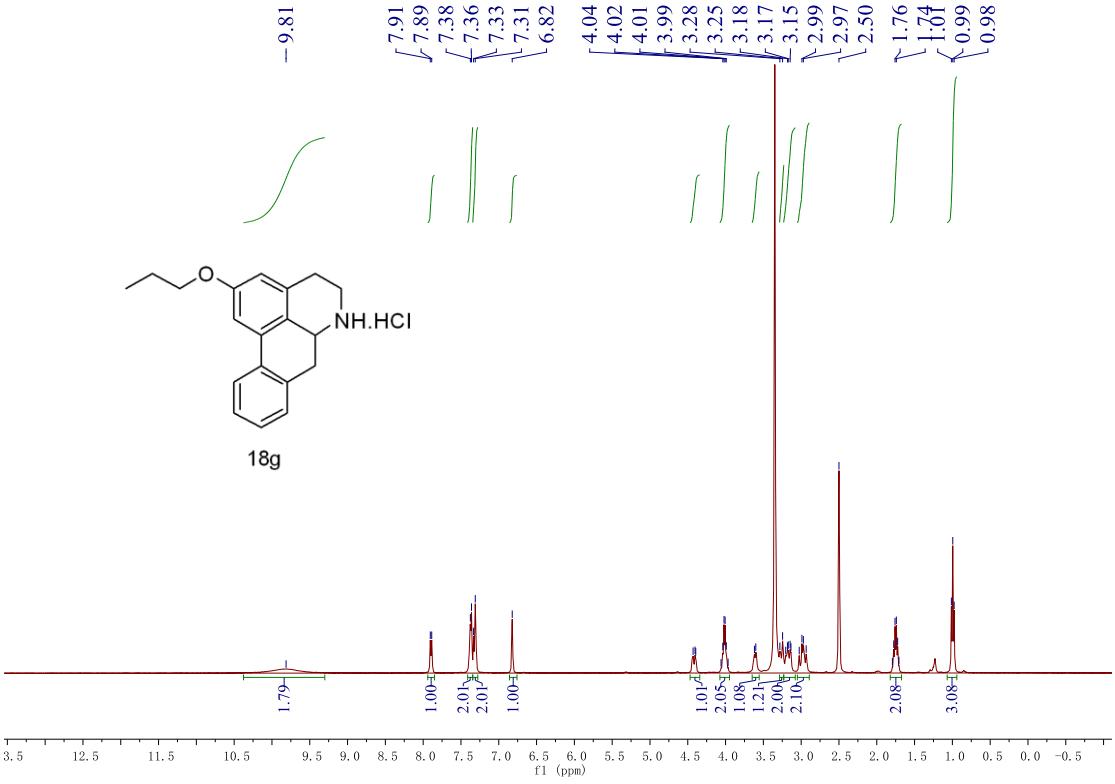
32.9
24.9
Cl
NH.HCl
18f
f1 (ppm)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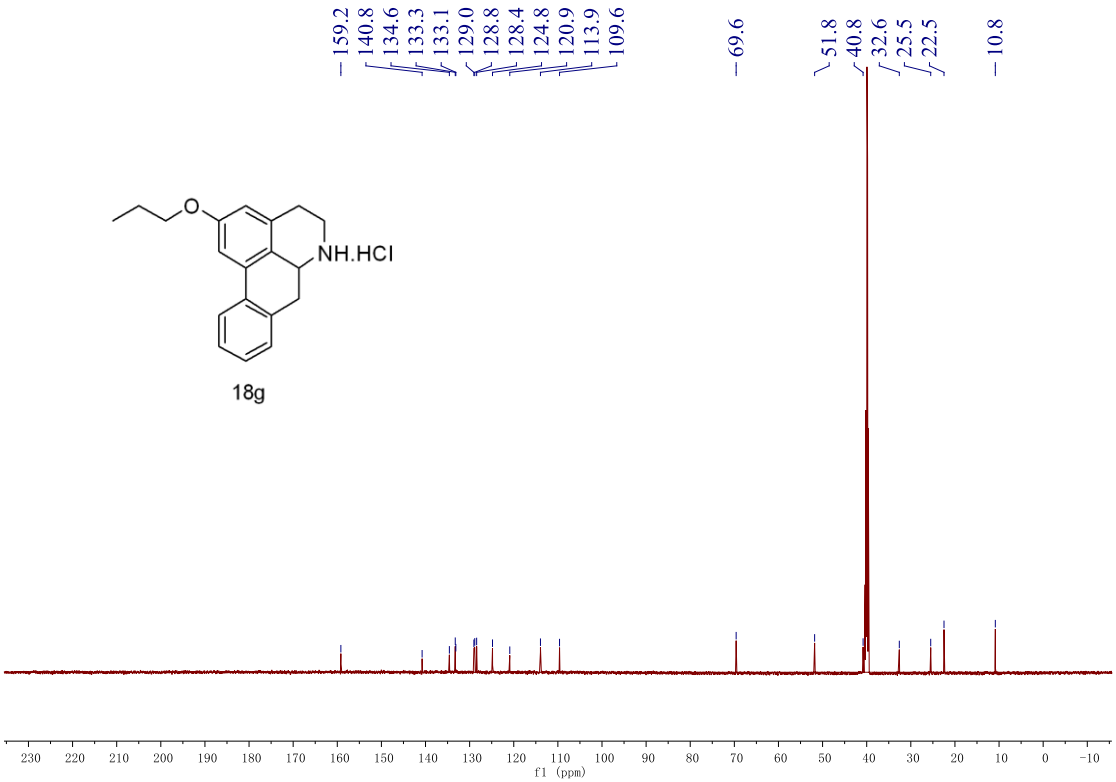
3.28
3.25
3.18
3.17
3.15
2.99
2.97
2.50
1.76
1.74
1.01
0.99
0.98
O
NH.HCl
18g
1.79
1.00
2.01
2.01
1.00
1.01
2.05
1.08
1.21
2.00
2.10
2.08
3.08
f1 (ppm)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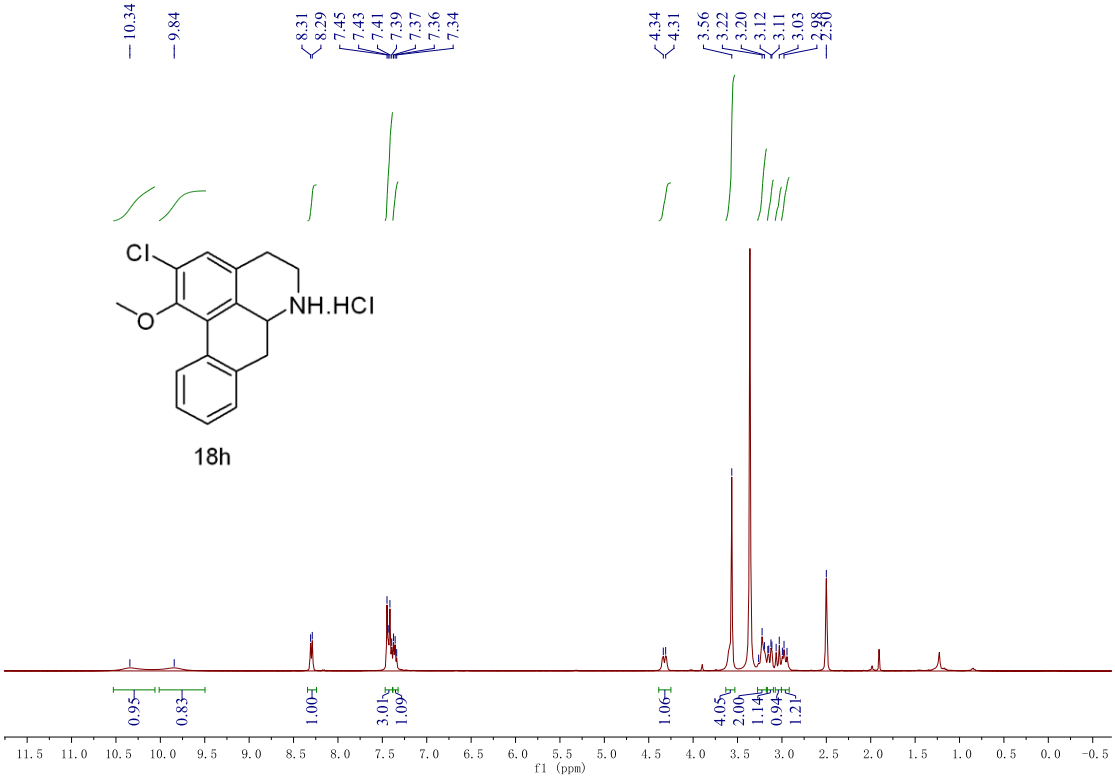
128.4
124.8
120.9
113.9
109.6
69.6
51.8
40.8
32.6
25.5
22.5
10.8
O
NH.HCl
18g
f1 (ppm)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7.36
7.34
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4.31
3.56
3.22
3.20
3.12
3.11
3.03
2.98
2.90
Cl
O
NH.HCl
18h
0.95
0.83
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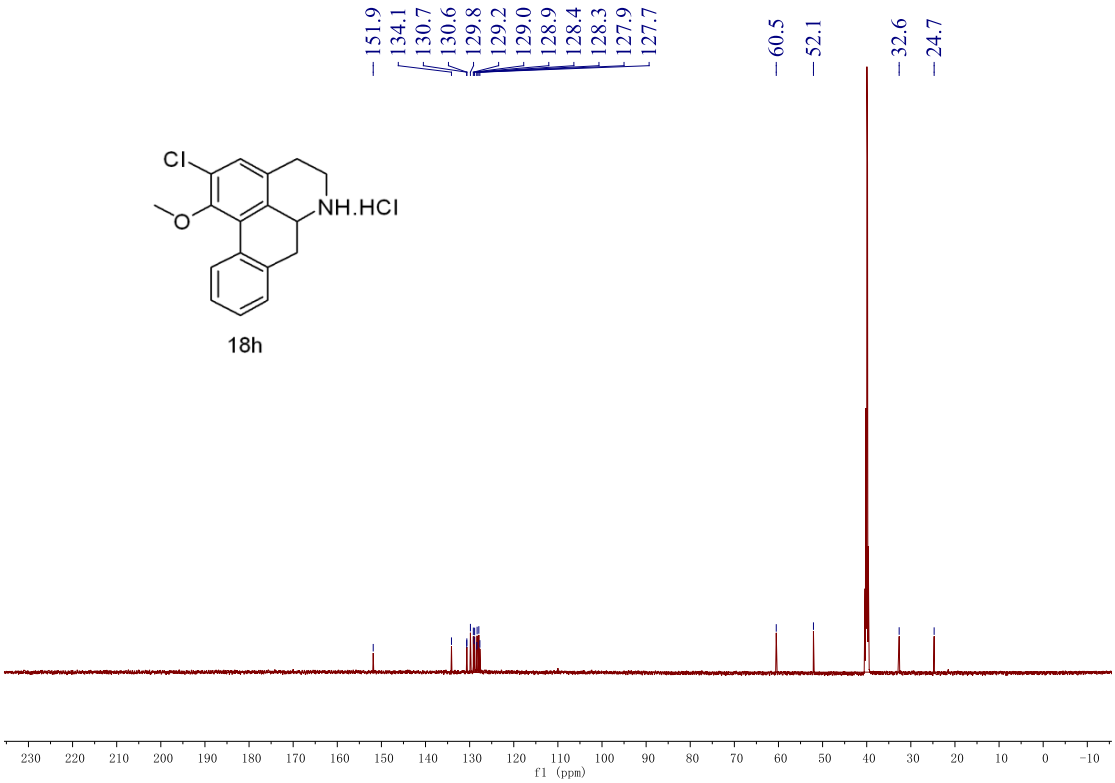
3.01
1.09
1.06
4.05
2.00
1.14
0.94
1.21
f1 (ppm)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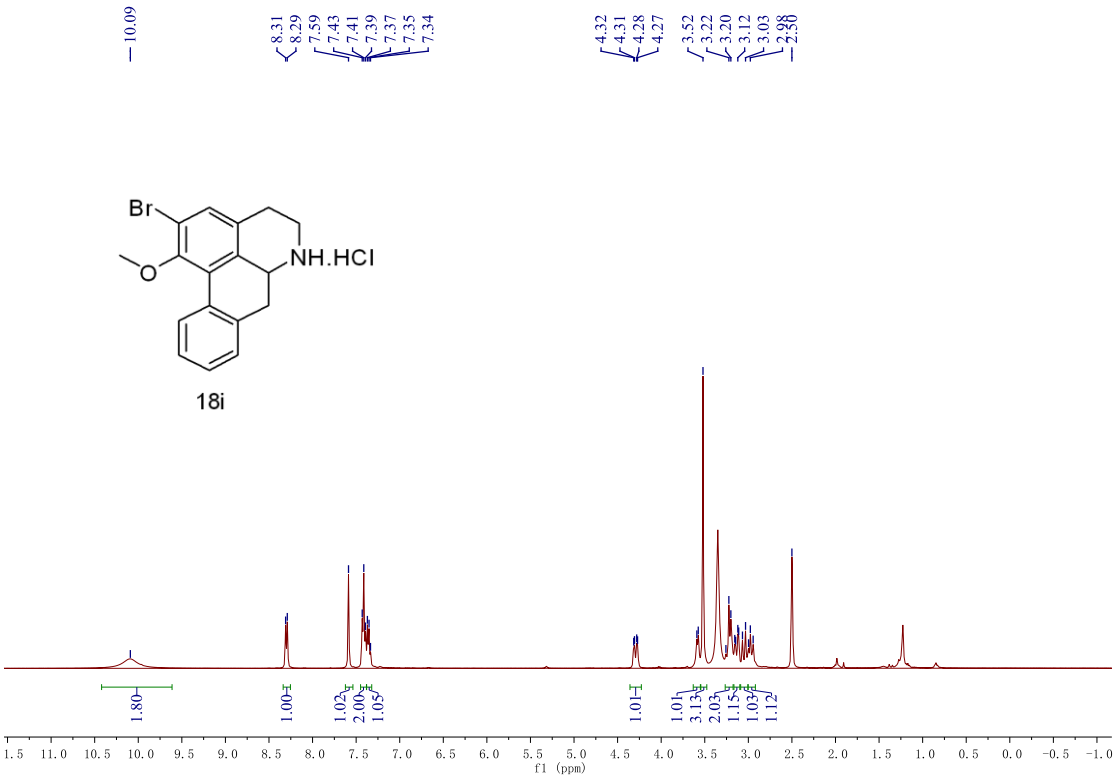
32.6
24.7
Cl
O
NH.HCl
18h
f1 (ppm)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7.43
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7.37
7.35
7.34
4.32
4.31
4.28
4.27
3.52
3.22
3.20
3.12
3.03
2.98
2.50
Br
O
NH.HCl
18i
1.80
1.00
1.02
2.00
1.05
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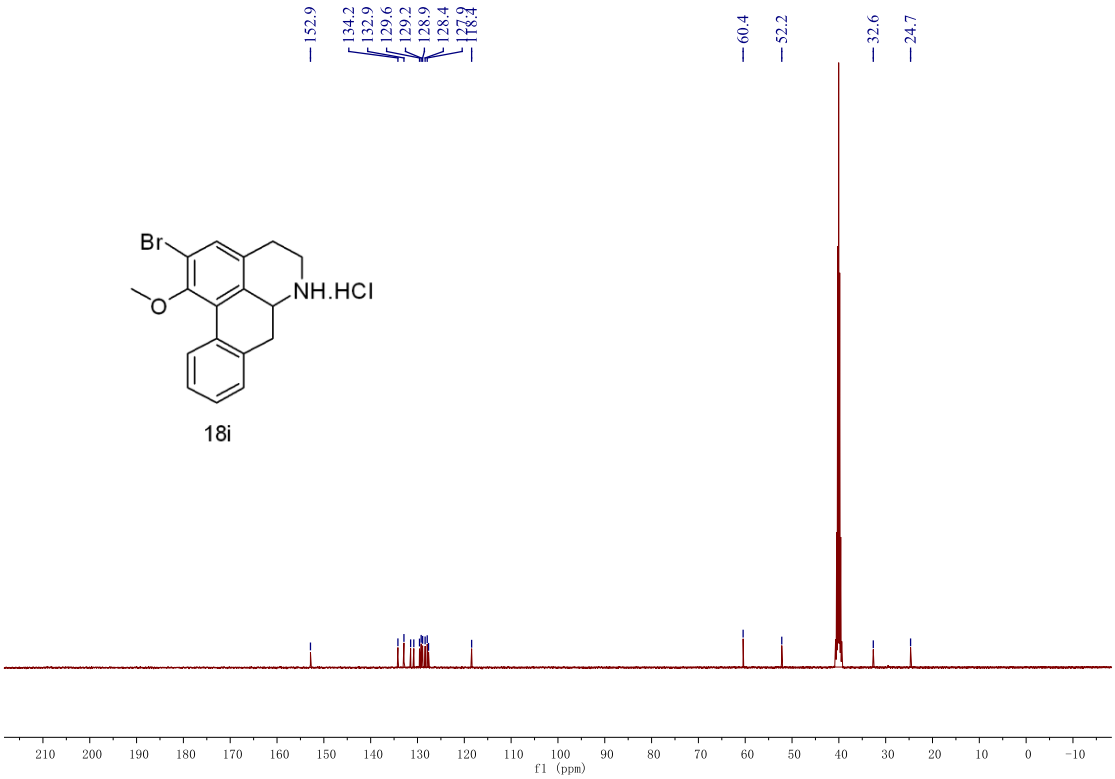
2.03
1.15
1.03
1.12
f1 (ppm)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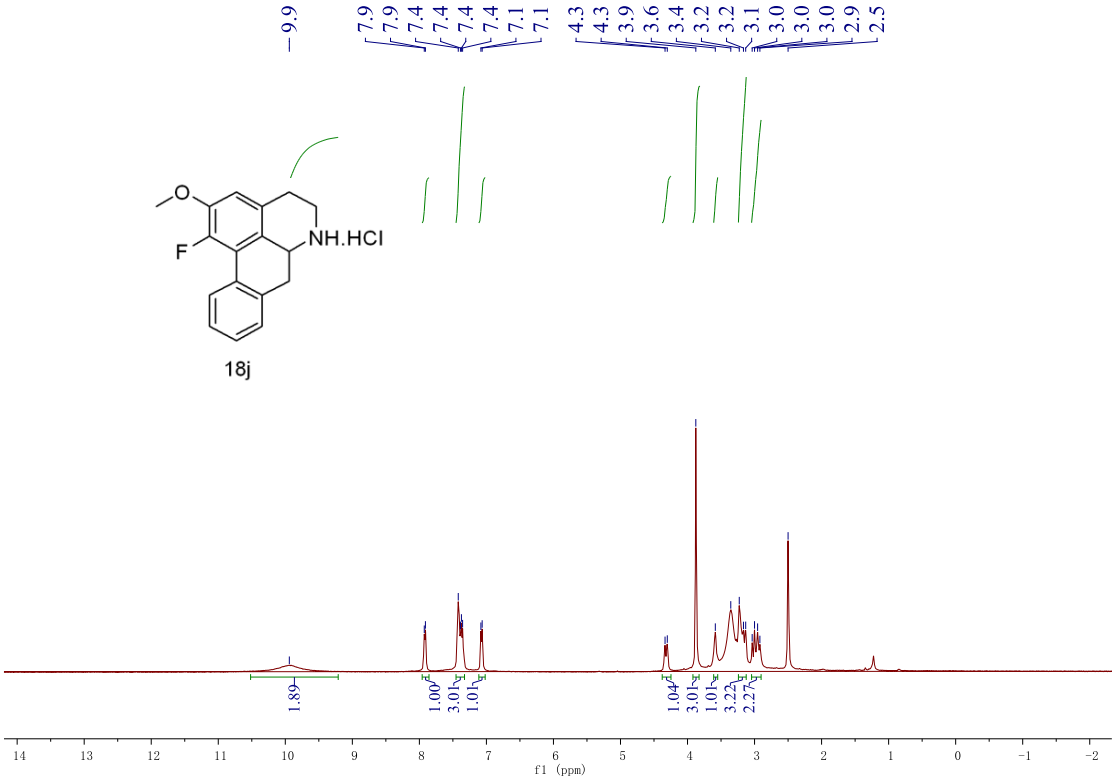
52.2
32.6
24.7
Br
O
NH.HCl
18i
f1 (ppm)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7.9
7.9
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7.4
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7.1
7.1
4.3
4.3
3.9
3.6
3.4
3.2
3.2
3.1
3.0
3.0
3.0
2.9
2.5
O
F
NH.HCl
18j
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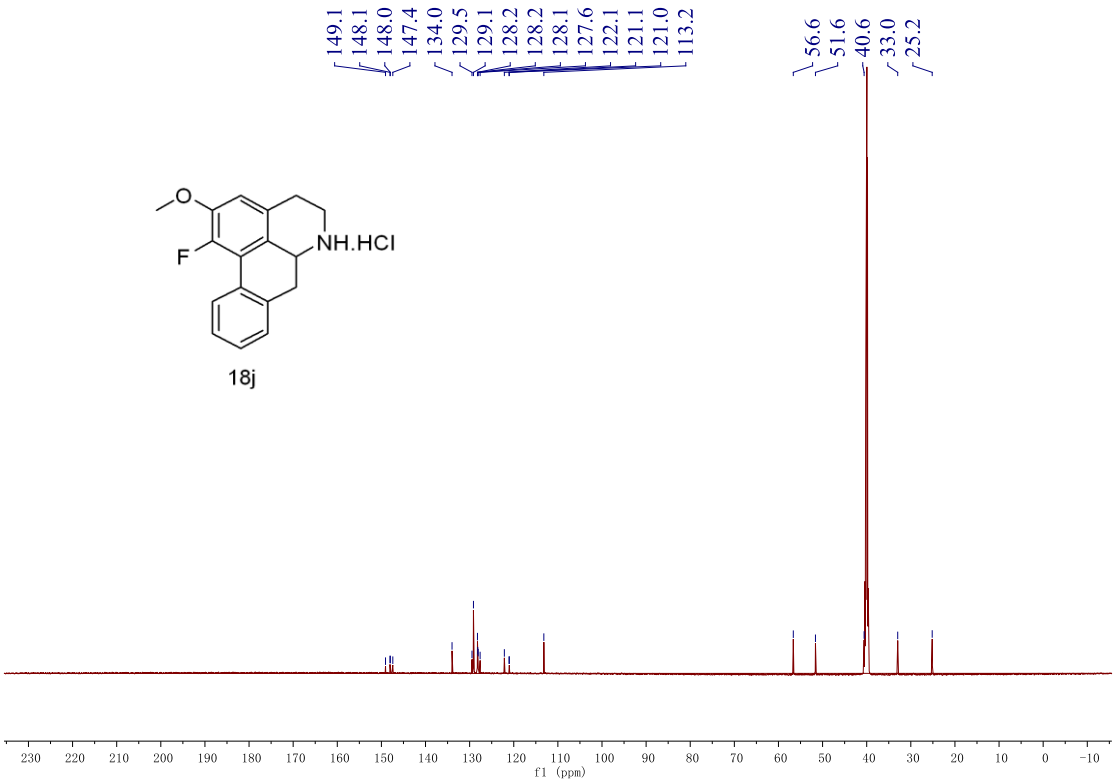
1.00
3.01
1.01
1.04
3.01
1.01
3.22
2.27
f1 (ppm)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148.0
147.4
134.0
129.5
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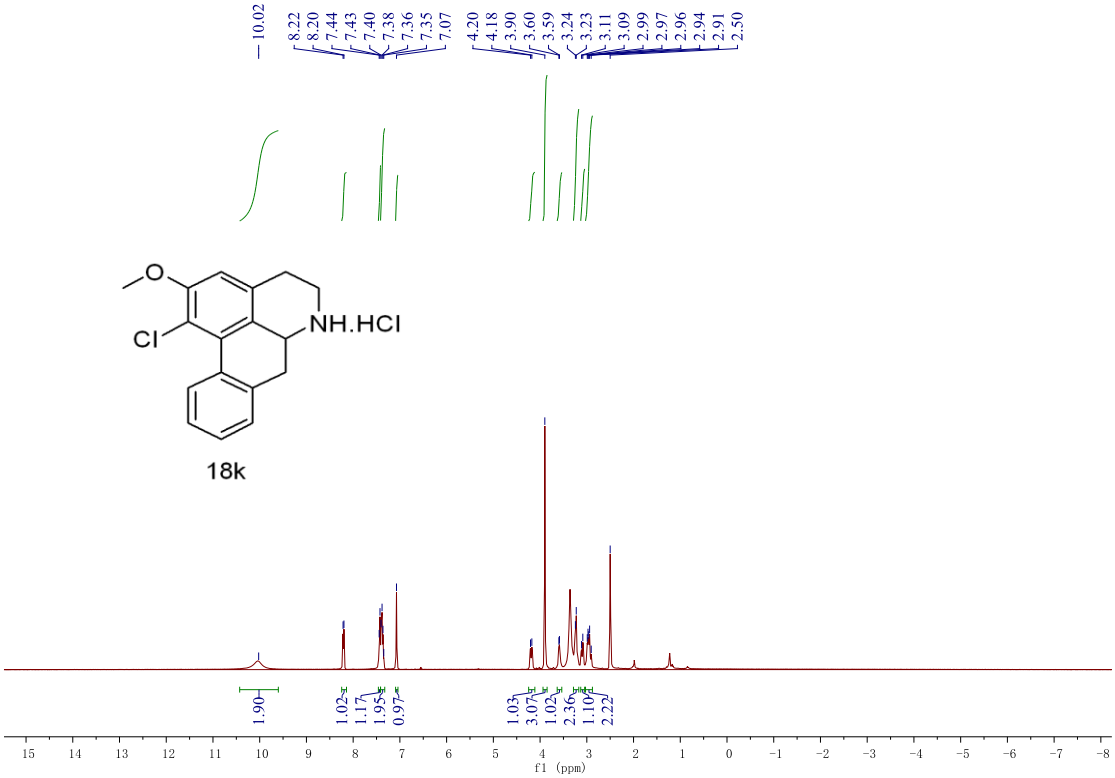
128.2
128.2
128.1
127.6
122.1
121.1
121.0
113.2
56.6
51.6
40.6
33.0
25.2
O
F
NH.HCl
18j
f1 (ppm)


10.02
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7.35
7.07
4.20
4.18
3.90
3.60
3.59
3.24
3.23
3.11
3.09
2.99
2.97
2.96
2.94
2.91
2.50
O
Cl
NH.HCl
18k
1.90
1.02
1.17
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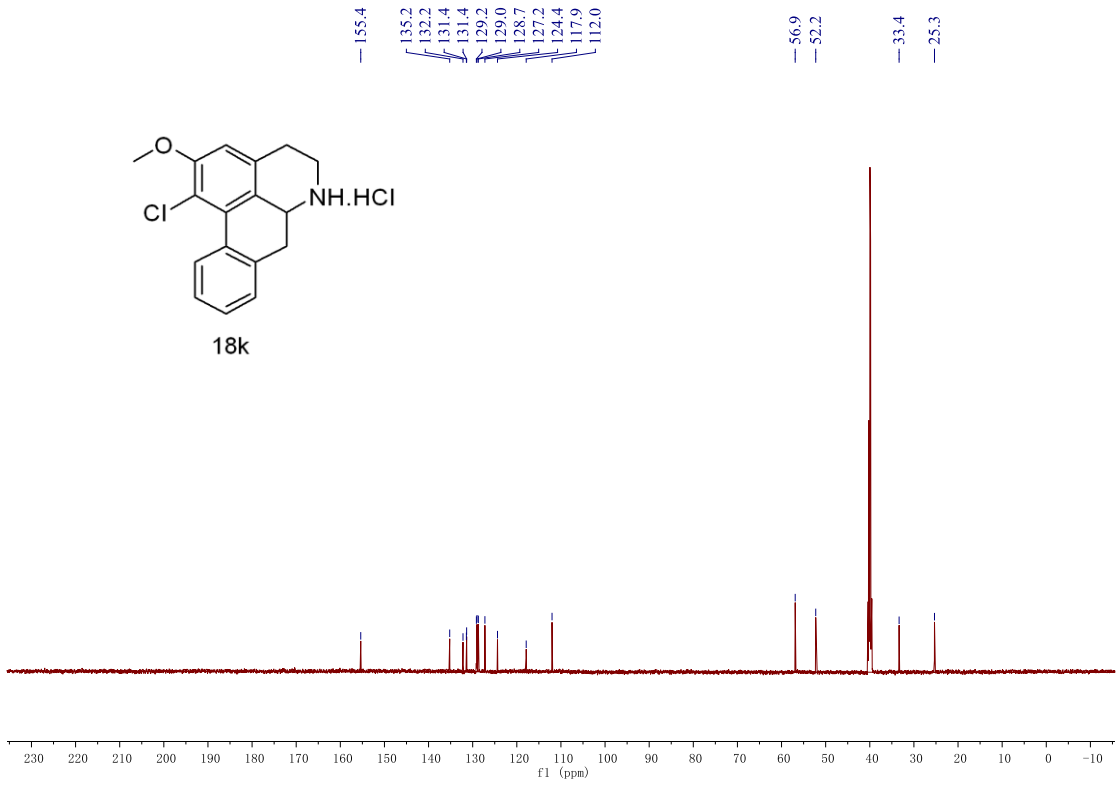
1.03
3.07
1.02
2.36
1.10
2.22
f1 (ppm)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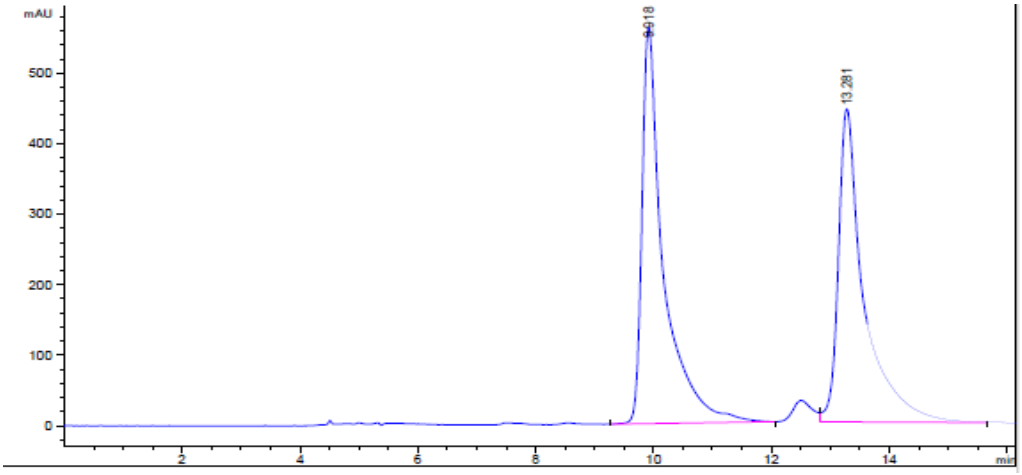
131.4
129.2
129.0
128.7
127.2
124.4
117.9
112.0
56.9
52.2
33.4
25.3
O
Cl
NH.HCl
18k
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

HPLC Spectra

Fig. S1. HPLC Spectra of Sample **13b**

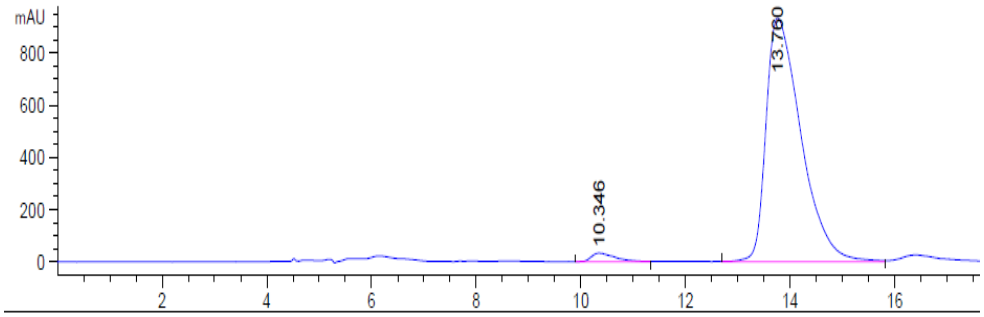
Column	CHIRALPAK® IC
Column size	4.6 mm ×250 mm L
Particle size	5 µm
Injection	20 µl
Temperature	25 ℃
Sample solution	0.5 mg/ mL in Isopropanol
HPLC equipment	Agilent LC3000



Peak No.	Time	Area %
1	9.918	51.6532
2	13.281	48.3468

Fig. S2. HPLC Spectra of Sample **(*R*)-13b**

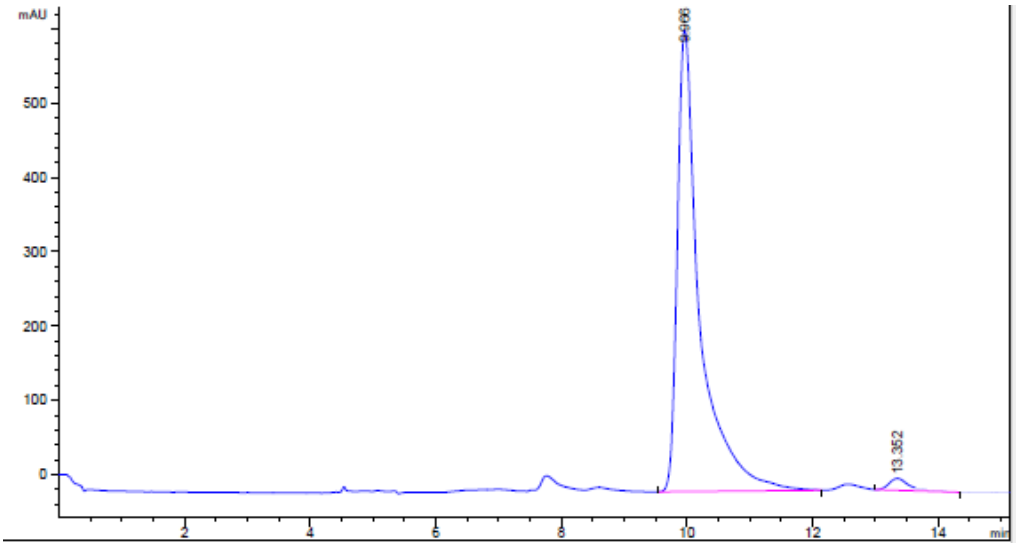
Column	CHIRALPAK® IC
Column size	4.6 mm ×250 mm L
Particle size	5 μm
Injection	20 μl
Temperature	25 ℃
Sample solution	0.5 mg/ mL in Isopropanol
HPLC equipment	Agilent LC3000



Peak No.	Time	Area %
1	10.346	2.2963
2	13.760	97.7037

Fig. S3. HPLC Spectra of Sample **(*S*)-13b**

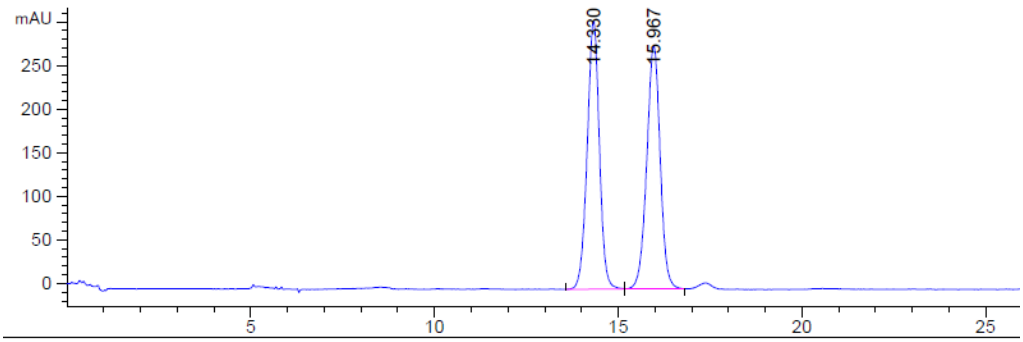
Column	CHIRALPAK® IC
Column size	4.6 mm ×250 mm L
Particle size	5 μm
Injection	20 μL
Temperature	25 ℃
Sample solution	0.5 mg/ mL in Isopropanol
HPLC equipment	Agilent LC3000



Peak No.	Time	Area %
1	9.966	97.7142
2	13.352	2.2858

Fig. S4. HPLC Spectra of Sample **18b**

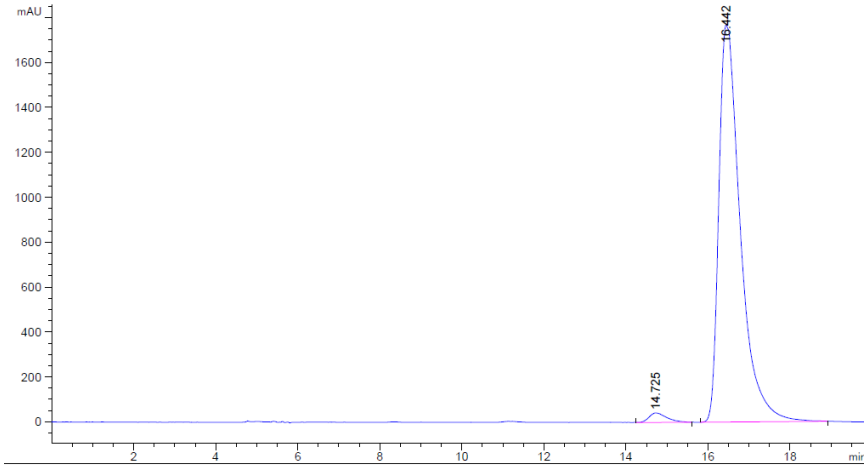
Column	CHIRALPAK® IC
Column size	4.6 mm ×250 mm L
Particle size	5 µm
Injection	20 µl
Temperature	25 ℃
Sample solution	0.5 mg/mL in Isopropanol
HPLC equipment	Agilent LC3000



Peak No.	Time	Area %
1	14.330	49.9742
2	15.967	50.0258

Fig. HPLC Spectra of Sample **(*S*)-18b**

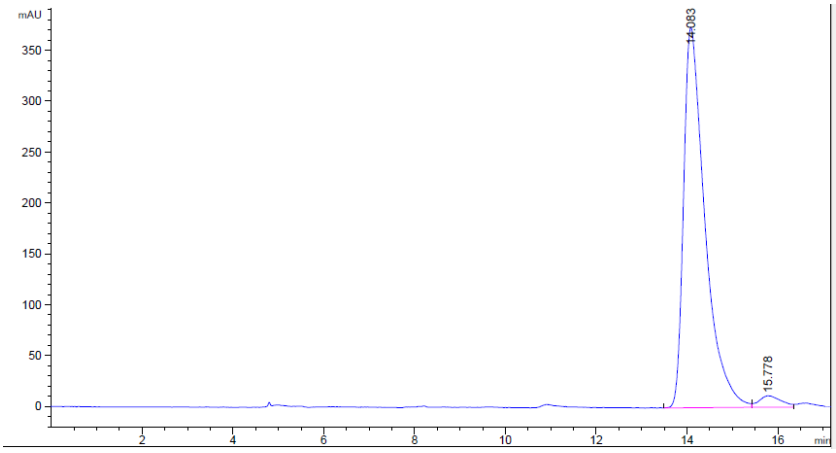
Column	CHIRALPAK® IC
Column size	4.6 mm ×250 mm L
Particle size	5 μm
Injection	20 μl
Temperature	25 ℃
Sample solution	0.5 mg/mL in Isopropanol
HPLC equipment	Agilent LC3000



Peak No.	Time	Area %
1	14.725	1.9455
2	16.442	98.0545

Fig.S6. HPLC Spectra of Sample **(*R*)-18b**

Column	CHIRALPAK® IC
Column size	4.6 mm ×250 mm L
Particle size	5 μm
Injection	20 μl
Temperature	25 ℃
Sample solution	0.5 mg/mL in Isopropanol
HPLC equipment	Agilent LC3000



Peak No.	Time	Area %
1	14.083	96.9800
2	15.778	3.0200